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COGNITIVE FUNCTIONING DURING THE TRANSITION FROM NORMAL AGING TO DEMENTIA

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"And in the end it's not the years in your life that count. It is the life in your years."

Abraham Lincoln

To Petri and Ludwig

ABSTRACT - ENGLISH

The general aim of this thesis was to address unresolved issues regarding cognitive functioning in preclinical dementia. Increasing the knowledge about the preclinical period of dementia might have important clinical implications. For example, it may facilitate early detection, and thereby increase the efficiency of available interventions.

All five empirical studies were based on data from the Kungsholmen Project – a longitudinal population-based study targeting persons living in the Kungsholmen parish of Stockholm, Sweden, who were ≥75 years on October 1, 1987.

In Study I and II, we investigated potential preclinical cognitive deficits in vascular dementia (VaD). It is well established that Alzheimer's disease (AD), the most common dementia disorder, is preceded by a preclinical phase with cognitive deficits. However, few studies have targeted the preclinical period in VaD, despite the fact that persons with VaD constitute approximately one fourth of dementia cases. In Study I, both preclinical VaD and preclinical AD persons showed cognitive impairment relative to controls on tasks assessing episodic memory 3 years before diagnosis. Although the results indicated a somewhat more widespread cognitive impairment in preclinical AD, there were no differences between the two dementia groups on any of the cognitive measures examined. In Study II, we observed an association between global cognitive functioning and incident VaD 3, but not 6, years before diagnosis. The association remained after controlling for demographic factors and history of vascular disorders.

In Study III and IV, we examined level and change in cognitive performance for preclinical dementia and impending death. We found that excluding persons with preclinical dementia from the impending death group resulted in markedly attenuated effects of mortality on cognitive performance. However, both impending death and preclinical dementia were associated with poorer cognitive performance at cross-section for all examined tasks. In Study III, the impending death persons showed no accelerated decline relative to the controls on a measure of global cognitive functioning, whereas the preclinical dementia persons declined twice as fast. Study IV focused on a smaller sample that had completed a cognitive test battery. In contrast to Study III, we observed significant terminal-decline effects for select cognitive tasks even after controlling for preclinical dementia. These effects were only observed for tasks in which the controls showed no significant decline.

In Study V, we examined the influence of preclinical dementia and impending death on the cross-sectional relationship between age and cognitive performance. We found that removal of the preclinical dementia and impending death groups from the original sample affected the cross-sectional age-cognition relationships relatively little.

In sum, cognitive deficits constitute an early sign of VaD as well as of AD, with the pattern of preclinical cognitive impairment being similar for the two disorders. We also found that a considerable proportion of the impending-death effect is accounted for by preclinical dementia. Further, accelerated cognitive decline is most often a sign of impending dementia, although accelerated decline may be observed in the years preceding death for tasks showing little age-related cognitive change. Finally, removal of persons in a preclinical phase of dementia or in close proximity to death affects the cross-sectional age-cognition relationship in an elderly sample relatively little, suggesting that the biological aging process exerts negative influences on cognitive functioning beyond those resulting from dementia and mortality.

ABSTRAKT - SVENSKA

Det övergripande syftet med denna avhandling var att undersöka kognitiva funktioner i preklinisk demens. Ökad kunskap om den prekliniska fasen i demens kan få stor klinisk betydelse. Till exempel skulle sådan kunskap kunna underlätta tidig upptäckt av en begynnande demenssjukdom, vilket kan göra tillgängliga interventioner mer effektiva.

Data till alla fem studierna är insamlade inom ramen för Kungsholmsprojektet, en longitudinell, populationsbaserad studie som omfattade alla personer boende i Kungsholmens församling i Stockholm, Sverige, som var ≥75 år 1:a oktober, 1987.

I Studie I och II undersökte vi potentiella prekliniska kognitiva nedsättningar i vaskulär demens (VaD). Det är allmänt vedertaget att Alzheimers sjukdom (AS), den vanligaste demenssjukdomen, föregås av en preklinisk fas med kognitiva nedsättningar. Få studier har emellertid fokuserat på den prekliniska perioden i VaD trots att personer med VaD utgör ca en fjärdedel av alla demensfall. I Studie I presterade både personer med preklinisk VaD och preklinisk AS sämre jämfört med en kontrollgrupp 3 år innan diagnos på uppgifter som mäter episodiskt minne. Även om resultaten tydde på en något bredare kognitiv nedsättning i preklinisk AS, så gick det inte att uppmäta några signifikanta skillnader mellan de två demensgrupperna på någon av de kognitiva uppgifterna. I Studie II observerade vi ett samband mellan global kognitiv förmåga och en framtida diagnos av VaD 3 år, men inte 6 år, före diagnos. Sambandet fanns kvar även efter att vi kontrollerat för demografiska faktorer och vaskulär sjukdomshistoria.

I Studie III och IV undersökte vi nivå och förändring av kognitiv prestation för preklinisk demens och förestående död. Vi fann att när personer med preklinisk demens exkluderades från gruppen med personer som skulle dö inom en snar framtid resulterade det i en betydligt förminskad effekt av förestående död på den kognitiva prestationen. Trots detta presterade både personer med preklinisk demens och förestående död på en lägre nivå än kontrollerna på samtliga kognitiva test. I Studie III förändrades personerna med förestående död i samma takt som kontrollerna på ett test av global kognitiv förmåga, medan personerna med preklinisk demens försämrades dubbelt så snabbt. Studie IV fokuserade på en mindre grupp personer som blivit testade med ett kognitivt testbatteri. Till skillnad från Studie III så försämrades personerna med förestående död i snabbare takt än kontrollerna även efter att vi kontrollerat för preklinisk demens, men bara för test där kontrollerna inte försämrades över tid.

I Studie V undersökte vi påverkan av preklinisk demens och förestående död på tvärsnittssambandet mellan ålder och kognitiv prestation. Vi fann att när personer med preklinisk demens och förestående död exkluderades från den totala gruppen deltagare, så påverkades sambandet mellan ålder och kognition relativt lite.

Sammanfattningsvis utgör kognitiv nedsättning ett tidigt tecken på VaD såväl som på AS, och det är samma kognitiva domäner som påverkas. Vi kunde också konstatera att en betydande del av effekten av förestående död på den kognitiva prestationen beror på preklinisk demens. Vidare är en accelererad kognitiv försämring oftast ett tecken på förestående demens. Förestående död kan emellertid också ge upphov till accelererad kognitiv försämring för uppgifter som normalt inte påverkas av ålder. Slutligen påverkas tvärsnittssambandet mellan ålder och kognition relativt lite av att man exkluderar personer med preklinisk demens och förestående död. Detta tyder på att biologiska åldrandeprocesser har ett negativt inflytande på den kognitiva prestationen utöver det som är direkt relaterat till demens och död.

LIST OF PUBLICATIONS

This thesis is based on the following original papers, referred to in the text by their Roman numerals:

I. Laukka, E. J., Jones, S., Small, B. J., Fratiglioni, L., & Bäckman, L. (2004). Similar patterns of cognitive deficits in the preclinical phases of vascular dementia and Alzheimer's disease. *Journal of the International Neuropsychological Society*, *10*, 382-391.

II. Laukka, E. J., Jones, S., Fratiglioni, L., & Bäckman, L. (2004). Cognitive functioning in preclinical vascular dementia: A 6-year follow-up. *Stroke*, *35*, 1805-1809.

III. Laukka, E. J., MacDonald, S. W. S., & Bäckman, L. (2006). Contrasting cognitive trajectories of impending death and preclinical dementia in the very old. *Neurology*, *66*, 833-838.

IV. Laukka, E. J., MacDonald, S. W. S., & Bäckman, L. (2006). *Terminal decline effects for select cognitive tasks after controlling for preclinical dementia.* Manuscript submitted for publication.

V. Bäckman, L., Laukka, E. J., Wahlin, Å., Small, B. J., & Fratiglioni, L. (2002). Influences of preclinical dementia and impending death on the magnitude of age-related cognitive deficits. *Psychology and Aging*, *17*, 435-442.

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ANOVA	Analysis of variance
APOE	Apolipoprotein E
CVD	Cerebrovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
HIS	Hachinski Ischemic Scale
ICD	International Classification of Disorders
KP	Kungsholmen Project
MMSE	Mini-Mental State Examination
NINCDS - ADRDA	National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association
NINDS - AIREN	National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences
VaD	Vascular dementia
VCI	Vascular cognitive impairment

TABLE OF CONTENTS

1 INTRODUCTION

We all grow older; this has and always will be the case. However, the extended life expectancy common today is a relatively new phenomenon. Both in Western societies and developing countries, the proportion of persons over the age of 65 is steadily increasing. This higher life expectancy reflects a positive development. However, it also brings new challenges. In particular, age-related diseases, such as dementia, have become increasingly relevant both for the individuals and for society. The number of dementia cases was estimated to be 24.3 million worldwide in 2005, with 4.6 million new cases every year (or one new case every 7 seconds; Ferri et al., 2005). A dementia disorder affects most aspects of a person's life, and also has a great impact on the lives of the person's relatives. Increasing the knowledge about the development of the disorder, how it can be identified at an early stage, and, of course, how it can be prevented or treated, could make a big difference for a large number of people. As dementing disorders develop over long periods of time, it is especially important to obtain more knowledge about the early phase of the disorder, when interventions may render the largest benefits. The period that precedes the dementia diagnosis, when the dementing process has started but the person does not yet fulfill the diagnostic criteria, is often termed the preclinical phase. Although this period has been the focus of numerous studies, many questions remain unanswered. This thesis aims to address some of these questions.

1.1 DEMENTIA

The term dementia derives from the Latin word for "out of one's mind". People have been aware of this condition since ancient times. It has been described as a second childhood, and has been considered a normal consequence of aging (Roman, 2002). Today we know that old age is not necessarily accompanied by poor cognitive functioning. The occurrence of dementia before age 60 is rare, but after age 70 both incidence and prevalence increase dramatically with age, with 1% prevalence at the age of 65 and 45% prevalence among those 95 years or older. Whether this age-related increase in dementia frequency continues into very advanced ages, with dementia being an inevitable feature of aging, remains an unresolved issue (Fratiglioni & Rocca, 2001; Fratiglioni, De Ronchi, & Agüero-Torres, 1999).

Dementia is commonly diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association, 1994). These criteria require memory impairment (with impaired ability to learn new information or recall previously learned information) and at least one of four additional cognitive disturbances: aphasia (language disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function), or deficits in executive functioning (e.g., planning, initiating, and suppressing a response). The cognitive deficits should cause significant impairment in social or occupational functioning, and represent significant decline from a previous level of functioning. Further, the cognitive deficits should not occur exclusively during the course of delirium.

1.1.1 Alzheimer's disease

Alzheimer's disease (AD) is the most common of the dementing disorders, constituting 50-70% of the cases in Western countries (Fratiglioni et al., 1999). The name emanates from Alois Alzheimer, the German psychiatrist and neuropathologist, who described the first case (Auguste D) in the early 20th century.

AD is characterized by progressive dementia, accompanied by structural and biochemical changes in the brain. These changes include neuronal and synaptic loss, intracellular aggregates of tau protein in neurofibrillary tangles, and extracellular deposits of β-amyloid protein in senile plaques (Wang et al., 2001). The onset is gradual, with memory deficits being the most prominent early sign. The first changes are typically found in medial-temporal lobe structures (Braak & Braak, 1991). Most research regarding the pathogenesis of AD has focused on either β-amyloid protein or microtubule-associated protein tau. Other mechanisms that have been suggested to play an important role are events related to apoptosis, oxidative stress, inflammation, calcium homeostasis, toxic, and vascular factors. However, what initiates the AD process and what factors play the biggest role in its progression is still largely unknown (Alafuzoff & Soininen, 2002).

Clinical criteria for receiving a diagnosis of AD have been established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) work group. Requirements for a diagnosis of probable AD include (a) diagnosed dementia with deficits in two or more areas of cognition, (b) progressive worsening of memory and other cognitive functions, (c) no disturbance of consciousness, (d) onset between ages 40 and 90 (most often after age 65), and (e) absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits. For a diagnosis of definite dementia, histopathologic evidence is required from a biopsy or autopsy to support the clinical diagnosis (McKhann et al., 1984).

1.1.2 Vascular dementia

Vascular dementia (VaD) is the second most common dementing disorder, representing around 20-30% of all dementia cases in Western countries (Fratiglioni el al., 1999). As the name implies, VaD is caused by pathologic changes in the vessels that lead to various forms of cerebrovascular disease (CVD). The onset may be sudden or gradual, and the progression is often stepwise as additional vascular events cause increasingly severe cognitive deficits. The clinical manifestation is heterogeneous and varies depending on the location of the vascular lesions. There are three main subtypes of VaD. *Multi-infarct dementia* is caused by multiple large complete brain infarcts, usually from large-vessel occlusions involving cortical and subcortical areas. *Strategic single-infarct dementia* results from small, localized ischemic damage in functionally important cortical and subcortical areas. *Small-vessel disease with dementia* is caused by cortical or subcortical lesions (including lacunes and white-matter lesions; Roman et al., 1993). In contrast to multi-infarct and strategic single-infarct dementia, small-vessel VaD has a more insidious onset, similar to that observed in AD.

Research criteria for a diagnosis of VaD have been put forward by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Research et l'Enseignement en Neurosciences (AIREN). A diagnosis of probable VaD is based on three requirements: (a) a dementia diagnosis, with impairment in memory and at least two other cognitive domains, (b) CVD confirmed by focal signs on neurologic examination and evidence of relevant CVD by brain imaging, and (c) a temporal relationship between the two disorders manifested by onset of dementia within 3 months following a recognized stroke, and/or abrupt deterioration in cognitive functions, and/or fluctuating, stepwise progression of cognitive deficits. In the absence of brain-imaging confirmation of CVD, a diagnosis of possible VaD can be made. As for AD, a definite diagnosis could only be made with biopsy or autopsy data (Roman et al., 1993).

Comparing different studies on VaD has been problematic because of the lack of uniform diagnostic criteria. The NINDS-AIREN criteria were one attempt to resolve this heterogeneity in diagnostic procedures, but several other diagnostic criteria are in use. Studies have shown that there is a large difference in the prevalence of VaD depending on which diagnostic criteria are employed (Chui et al., 2000). Recently, increasing attention has been directed at subcortical ischaemic VaD, with small-vessel disease as the primary vascular etiology. This variant is supposed to be more clinically homogeneous than other types of VaD, and thus more suitable for clinical trials (Erkinjuntti et al., 2000).

Making a differential diagnosis between VaD and AD is not always a straightforward task. In addition to the problem of several diagnostic criteria for VaD being used in parallel, there is also the issue of overlap between the two types of dementia pathology. Autopsy evidence suggests that cerebrovascular pathology is present in 30% of the AD cases, and that some types of vascular lesions (e.g., white-matter lesions) are found in almost all cases (Kalaria & Ballard, 1999). In a recent study based on autopsy data, contaminant AD pathology was present in 77% of clinically diagnosed VaD patients, with pure vascular pathology being very uncommon (Barker et al., 2002). Separating the two dementia disorders is especially difficult in the oldest age groups, as mixed pathologies become increasingly common with advancing age (Agüero-Torres, Winblad, & Fratiglioni, 1999).

1.2   COGNITION

The term cognition refers to the mental activities involved in acquiring and processing information (Colman, 2006). It includes activities that we are constantly involved in, like perception, memory, and reasoning. The next section gives an overview of the cognitive domains examined in the present thesis.

1.2.1   Global cognitive functioning

Global measures of cognition may be used both to index a person's general level of cognitive functioning and as a screening tool. In the Kungsholmen Project (KP), on which this thesis is based, the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) was used as a measure of global cognitive ability. The

MMSE is a screening instrument for cognitive impairment frequently used as a rapid way of assessing cognitive functioning in elderly persons. It includes 11 subscales, targeting a range of cognitive domains like episodic memory, attention, language, and visuospatial skill. Each subscale gives a score of 1 to 5 and the maximum total score is 30.

1.2.2 Memory

Memory is the cognitive function we use to encode, store, and retrieve information. It can be divided into two broad categories, short-term and long-term memory (see e.g., Schacter & Tulving, 1994, for an overview).

1.2.2.1 Short-term memory

Short-term memory deals with temporary storage of information. This information is not necessarily stored in long-term memory but might be forgotten the next second. Short-term memory can be further divided into primary memory, that deals with passive holding of information (e.g., remembering a phone number while you are dialing it), and working memory (Baddeley, 1986), that involves both holding and processing of information (e.g., solving a mathematical problem in several steps). In this thesis, Digit Span (Wechsler, 1981) was used to assess short-term memory. This task involves repeating a series of numbers in the same order (*Digit Span-forward,* primary memory), or in the reverse order (*Digit Span-backward,* primary and working memory), as they were presented.

1.2.2.2 Long-term memory

Long-term memory can be divided into four subsystems (Schacter & Tulving, 1994). Procedural memory is involved in the performance of automatized behavior (e.g., riding a bike). The perceptual representation system is used in the identification of objects in our environment. These forms of memory do not involve conscious awareness. Semantic memory deals with factual knowledge that may have been acquired over a long period of time (e.g., knowing the name of Sweden's prime minister). In contrast, episodic memory concerns personally experienced events, encoded at a specific time and place. Episodic retrieval is unique in the sense that it involves mental time travel, when you re-experience your personal past (Wheeler, Stuss, & Tulving, 1997). Episodic memory is the form of memory most sensitive to aging and it is assessed in most longitudinal studies of aging and cognition. In this thesis, I only consider episodic memory and not the other three subsystems.

In the Kungsholmen cognitive battery, episodic memory was assessed by a face recognition task and three different word lists (Bäckman & Forsell, 1994). In the face recognition task, 40 photographs of famous faces were presented at a rate of 5 seconds/face. Following presentation, there was a self-paced recognition task in which the 40 target faces were presented along with an equal number of distractors. The *face recognition* score denotes number of hits minus number of false alarms. The three word lists were constructed to vary with regard to the degree of cognitive support provided at encoding and retrieval. For the first word list, 12 unrelated words were presented at a rate of 2 seconds/word, followed by a 2-minute free recall task and a self-paced recognition task. The second word list also comprised 12 unrelated words. It was administered in the same way as the first word list, except that the presentation rate was instead 5 seconds/word. Performance on the two unrelated word lists was aggregated into one *random recall* and one *word recognition* composite

4

score. The third word list consisted of 12 words organized into four taxonomic categories (furniture, professions, musical instruments, and pieces of clothing). Following a free recall task, a cued recall task was administered in which the four taxonomic categories were provided as cues. Performance was recorded for *organized recall*, a composite score of free and total (free+cued) recall.

The Kungsholmen cognitive battery was administered in two different test orders, so that the order of the tasks varied among participants and testing occasions. There were also five different versions of the word lists and five different presentation orders of the face recognition task, so that the same person would never be tested twice in the exact same way.

1.2.3   Visuospatial ability

Visuospatial ability includes analyzing spatial information (e.g., reading a map) as well as constructional skills (e.g., drawing a complex figure). In the Kungsholmen battery, visuospatial ability was assessed with two tasks. The clock test (Christensen, 1984) consisted of two parts; *clock reading*, which involved reading the time from five different clocks; and *clock setting*, which involved drawing the hands on five empty clock faces to indicate given times. For *Block Design* (Wechsler, 1981), the task was to reproduce given patterns with three-dimensional blocks colored in red and white. A modified version with a lower level of difficulty was used in order to enable the assessment of demented persons as well as healthy elderly adults.

1.2.4   Verbal ability

Verbal ability involves the comprehension and production of language. In the Kungsholmen battery, verbal ability was assessed with three verbal fluency tasks (Lezak, 1995). In *letter fluency*, the person was asked to produce as many words as possible beginning with a specific letter (n or s) during one minute. In *category fluency,* the task was instead to generate as many grocery store items as possible. Note that, although these tasks have a heavy language component, other cognitive functions are involved as well, including short-term memory, semantic memory, mental speed, and executive functioning.

1.3   AGING AND COGNITION

How cognitive functioning is affected by aging is a question that has attracted a lot of attention, as this concerns most of us. The study of aging and cognition is interesting from a theoretical perspective. However, it is also important from a clinical point of view, as knowledge about age-related cognitive change in the absence of disease renders possible the identification of pathological patterns of change.

It is generally known that old age is associated with poorer cognitive functioning. Elderly persons' most frequent complaints concern problems with their memory. Indeed, research has shown that memory performance declines with advancing adult age. However, some forms of memory are quite resistant to age changes. A meta-analysis of cross-sectional studies comparing measures of vocabulary scores, reflecting semantic memory, for young (mean age = 21 years) and old (mean age = 70 years) adults actually found a positive effect of age. The effect size was $d = 0.80$ favoring the old, with a larger effect size for multiple-choice tasks ($d = 0.93$) compared to production tests ($d = 0.68$; Verhaeghen, 2003). According to convention,

an effect size of 0.20 represents a small effect, 0.50 a medium effect, and 0.80 a large effect (Cohen, 1992). However, it should be remembered that cohort effects and bias in the recruitment of samples might influence the results of cross-sectional studies. For semantic memory, level of education seems to be a particularly important factor. To illustrate this, the positive age effect for multiple-choice tasks disappeared when education was taken into account, as the older participants had a higher level of education (Verhaeghen, 2003).

Although older adults generally show stable or improved performance in vocabulary tasks, they often have difficulties in remembering proper names and generating words (Bäckman, Small, & Wahlin, 2001). Moreover, even more age-resistant semantic memory tasks appear to decline in the highest age groups. For example, cross-sectional data from the Betula project, a Swedish longitudinal study of aging and cognition, show increased performance in vocabulary and general knowledge from 35 to 60 years, with decreased performance after that age (Nilsson, 2003).

Being the most age-sensitive type of memory, episodic memory shows dramatic decreases in performance as a function of age. Cross-sectional data, again from the Betula project, demonstrate steady decline in episodic memory performance for the age range 35 to 80 years (Nilsson, 2003). Further, a meta-analysis contrasting young (mean age = 22 years) and old (mean age = 70 years) adults reported effect sizes ranging from $d = 0.7$ to $d = 1.0$ favoring young adults for different episodic recall tasks (Verhaeghen, Marcoen, & Goossens, 1993). However, the amount of cognitive resources required to perform a task seems to be of importance for the size of the age effect. For example, one study using picture recognition tasks, involving a high degree of cognitive support, reported no age differences in episodic memory performance (Park, Puglisi, & Smith, 1986).

Also for short-term memory, the findings depend on the nature of the task used. Measures of primary memory often yield small or non-existent age-related differences, whereas more cognitively demanding working memory tasks show robust age-related deficits (Bäckman, Small, & Wahlin, 2001). However, the meta-analysis on aging and memory described above showed comparable effect sizes (ds = 0.4) for Digit Span-forward (primary memory) and Digit Span-backward (primary and working memory). Meanwhile, a larger effect size, again favoring young adults, was obtained for other working memory measures ($d = 0.8$; Verhaeghen et al., 1993).

Aging affects many cognitive abilities in addition to memory. A distinction is often made between crystallized and fluid intelligence. Crystallized abilities are dependent on previous experience and the accumulation of knowledge in long-term memory (e.g., vocabulary), whereas fluid abilities are dependent on reasoning abilities and speed of processing (e.g., visuospatial ability). In general, crystallized abilities show relative stability with increasing age, whereas fluid abilities show robust and gradual age-related change across the life span (Bäckman, Small, Wahlin, & Larsson, 2000). However, perhaps the most consistent finding in the cognitive aging literature is the decline of speed of processing with increasing age, often believed to start in the early twenties (e.g., Park et al., 1996). Some have even argued that age-related variance in fluid intelligence and memory is to a large extent explained by age-related decline in processing speed (Salthouse, 1996).

To summarize the findings on aging and cognition, older adults are quite efficient in utilizing preexisting knowledge structures, but not when fast and efficient processing of novel information is required.

The bulk of studies on cognitive aging consist of cross-sectional studies, comparing different age cohorts assessed at the same testing occasion. However, persons belonging to different age groups might also differ in other respects, such as level of educational attainment. Thus, cohort effects in cross-sectional studies might lead to overestimation of the magnitude of age-related change. Although longitudinal studies suffer from other problems, such as selective attrition and practice effects, it is necessary to evaluate theories of cognitive aging in longitudinal data sets (Sliwinski & Buschke, 1999). Notably, studies that have followed the same individuals over time render somewhat different results regarding the patterns of age-related change compared to cross-sectional studies. A recent study compared patterns of change obtained from cross-sectional and longitudinal data for semantic and episodic memory in the Betula study (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). The authors found similar patterns for cross-sectional and longitudinal data for the ages 60-85, with reliable decline in both semantic and episodic memory. However, for younger ages (35-60 years), the patterns differed. Whereas cross-sectional data indicated age-related decline in episodic memory performance, longitudinal practice-adjusted data indicated stability. For semantic memory, cross-sectional data pointed at stability, whereas longitudinal data indicated improved semantic memory performance for the same age range. The discrepant findings appeared to be due to cohort differences in educational attainment (Rönnlund et al., 2005).

1.4 COGNITIVE FUNCTIONING IN CLOSE PROXIMITY TO DEATH

As described in the previous section, advancing age is associated with cognitive decline. However, not everybody shows decline in cognitive functioning, and the rate of age-related change varies greatly among individuals (Wilson et al., 2002). One explanation for this heterogeneity is that decline in cognitive function might be more strongly related to time to death than to chronological age. The terminal-decline hypothesis states that a large proportion of the variability in cognitive performance among elderly persons can be accounted for by a given individual's proximity to death (Kleemeier, 1962).

Numerous studies have demonstrated cross-sectional effects of impending death on cognition for a range of cognitive abilities, such as primary memory (Johansson & Berg, 1989), episodic memory (Hassing et al., 2002), verbal ability (Rabbitt et al., 2002), visuospatial ability (Small & Bäckman, 1997), speed (Bosworth, Schaie, Willis, & Siegler, 1999), and global cognitive functioning (Anstey, Luszcz, Giles & Andrews, 2001). A distinction is sometimes made between terminal decline and terminal drop, with terminal decline representing a steady linear decline, and terminal drop representing curvilinear decline prior to death (Palmore & Cleveland, 1976). Addressing the question of the shape of cognitive decline in proximity to death is, however, a complicated task, requiring multiple cognitive assessments prior to death. As a result, relatively few studies have examined the effect of impending death on cognitive change (Bosworth & Siegler, 2002). However, two recent longitudinal studies on cognitive functioning in close proximity to death observed accelerated, although

linear, rates of cognitive decline 3.5 (Wilson, Beckett, Bienias, Evans, & Bennett, 2003) and 8 years (Sliwinski et al., 2006) prior to death, respectively.

It has yet to be determined whether the underlying mechanisms causing the mortality-related cognitive deficits reflect the influence of one or several specific diseases or a more general biological systems breakdown (Bäckman & MacDonald, 2006; Berg, 1996; Small & Bäckman, 1999). One disease that is closely connected to death is dementia. First, the occurrence of both death and dementia is strongly related to age. Second, both impending death (e.g., Small & Bäckman 1987) and preclinical dementia (e.g., Linn et al., 1995) have been associated with impaired cognitive functioning. Furthermore, dementia is a strong predictor of mortality (Agüero-Torres et al., 1999; Jagger et al., 2000; Tschanz et al., 2004). Despite this apparent association, surprisingly few studies have examined the effect of impending death and dementia on cognition within the same study.

Two recent studies examining the effect of proximity to death on intraindividual change in cognitive functioning reported strikingly different rates of cognitive change attributable to terminal decline (Wilson et al., 2003; Johansson et al., 2004). A key difference between these two studies is that the one that reported faster decline (Wilson et al., 2003) had excluded prevalent dementia cases solely at baseline, whereas the study reporting more modest decline had continuously excluded new dementia cases throughout the study (Johansson et al., 2004). This raises the question of whether preclinical dementia might be an important factor in explaining terminal-decline effects on cognition.

Besides the issue of what causes the terminal-decline effect, there are also unanswered questions regarding the conditions under which such effects might be expected. For example, it has been discussed whether the age of the elderly persons examined would affect the size of the impending-death effect. Given that older age is related to a higher mortality risk, it has been argued that the differences between survivors and decedents should diminish with age (Riegel & Riegel, 1972). Another issue under discussion is whether the cognitive domain assessed (e.g., crystallized vs. fluid intelligence) matters for the size of the mortality-related cognitive deficits (Bosworth & Siegler, 2002). Level of difficulty might represent another important factor, as terminal-decline effects might be more easily observed for tasks showing little age-related change (White & Cunningham, 1988; Small & Bäckman, 1999).

1.5 COGNITIVE FUNCTIONING IN PRECLINICAL DEMENTIA

The development of a dementia disorder is a process that takes years or maybe even decades. The period when cognitive deficits may be detected, although the person does not fulfill the diagnostic criteria for dementia, is often called the preclinical phase. During this transition period, the brain is affected by the pathological alterations but the point at which all diagnostic criteria are met has not yet been reached. A large number of studies have demonstrated a preclinical phase with cognitive deficits in AD (see next section). However, fewer studies have focused on VaD, despite the fact that persons with VaD constitute approximately one fourth of the dementia cases.

Preclinical dementia can be studied by identifying a large number of nondemented elderly persons, following them over time, and identifying new dementia cases at subsequent follow-up assessments. Cognitive performance of the persons who will later develop dementia may then be compared to that of individuals who will remain nondemented during the follow-up period. This means that studies concerning preclinical dementia involve persons who with 100% certainty will develop dementia.

More recently, a new concept has emerged, that also concerns the transitional stage between normal aging and dementia. The classification Mild Cognitive Impairment (MCI) seeks to identify persons with a high risk of developing dementia in the near future. Thus, studies on MCI are prospective in nature, where persons with impaired cognition are identified at baseline and followed over time to see whether they develop dementia. The manifestation of cognitive impairment in MCI could be impaired memory functioning (amnestic MCI), mild impairment in multiple cognitive domains, or impairment in a single cognitive domain other than memory (Petersen et al., 2001). Criteria for amnestic MCI require (a) presence of memory complaint (preferably corroborated by an informant), (b) impaired memory function for age and educational level, (c) preserved general cognitive function, (d) intact activities of daily living, and (e) absence of dementia (Petersen et al., 2001). It has been suggested that amnestic MCI represents a prodromal form of AD, although also persons with mild impairment in multiple domains (including memory) have a high likelihood of progressing to AD. A diagnosis of VaD, on the other hand, may be preceded by mild impairment in multiple cognitive domains, with or without memory impairment (Petersen, 2004). Although studies have shown that persons with MCI have a high risk of progressing to dementia, this category is very heterogeneous (Larrieu et al., 2002; Ganguli, Dodge, Shen, & DeKosky, 2004). To illustrate this, cognitive impairment at a given point in time has been associated with an equal risk of dementia, death, and remaining stable within the next few years (Bennett et al., 2002; Palmer, Wang, Bäckman, Winblad, & Fratiglioni, 2002). Clearly, many questions remain to be answered regarding cognitive functioning during the period preceding a dementia diagnosis.

One reason why studies of preclinical dementia are so important is that this is an excellent way of gaining knowledge about how the disorder develops. We know that the development of dementia is a long process and once a person is diagnosed, the brain has already undergone substantial structural and functional change. By studying the early phase of the disorder, we can learn more about what parts of the brain are affected at different stages. Second, studying the preclinical phase of dementia could help us identify early signs of the disorder. It is crucial to be able to detect persons about to develop dementia at the earliest possible stage, when interventions would be most effective. By initializing treatment at an early stage, we might postpone the onset of the dementia disorder. Finally, it is important to know the natural development of cognitive functioning prior to a dementia diagnosis in order to evaluate existing and future interventions.

1.5.1 Cognitive functioning in preclinical AD

As stated above, most studies on cognitive functioning in preclinical dementia have concerned AD. It is well established that a diagnosis of AD is associated with impaired

cognitive performance in the years preceding diagnosis for a range of cognitive domains (e.g., Howieson et al., 1997; Jacobs et al., 1995; Linn et al., 1995; Small, Herlitz, Fratiglioni, Almkvist, & Bäckman, 1997). Recently, the findings from 47 studies were summarized in a meta-analysis (Bäckman, Jones, Berger, Laukka, & Small, 2005). Figure 1 shows the effect sizes associated with the cognitive domains examined. Preclinical dementia affected all cognitive domains except primary memory. Large effect sizes were observed for perceptual speed, executive functioning, and episodic memory alike, whereas verbal ability, visuospatial ability, and attention yielded medium effect sizes. Episodic memory deficits are considered a cardinal feature of AD, and indeed a large effect size was observed for episodic memory, comparable to that observed when contrasting young and old adults as described earlier (Verhaeghen et al., 1993). However, the cognitive deficit in preclinical AD was not limited to the episodic memory domain. The fact that a large effect was also observed for global cognitive ability underscores the finding of a general cognitive deficit in preclinical AD. It is of interest to note that the cognitive domains most affected in preclinical AD (speed, executive functioning, episodic memory) are the same cognitive domains that are most affected by normal aging. This indicates continuity in patterns of cognitive impairment from normal aging to preclinical AD (Bäckman et al., 2005).
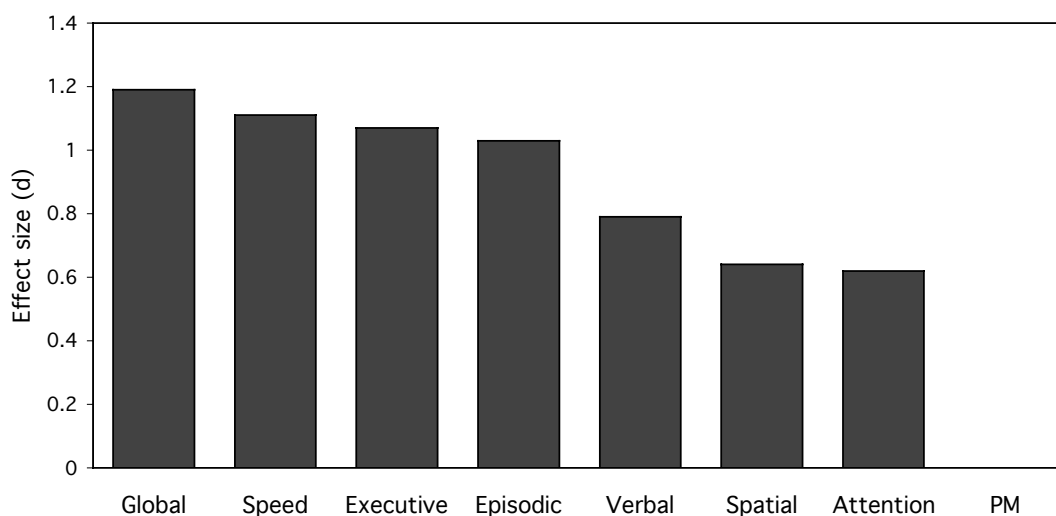
Figure 1. Preclinical deficits in AD for global cognitive ability and seven specific cognitive domains (adapted from Bäckman et al., 2005). PM = primary memory.

The observation that episodic memory deficits can be detected years before an AD diagnosis has been paralleled with neuroimaging findings of volume reductions of the hippocampus (Jack et al., 2000) and the enthorhinal cortex (Killiany et al., 2002) in preclinical AD. There are also autopsy studies of AD showing involvement of medial-temporal lobe structures, especially the enthorhinal cortex and hippocampus, early in the disease process, before a diagnosis can be rendered (Braak & Braak, 1991). Given the importance of the hippocampus for episodic memory functioning (Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996; Vargha-Khadem et al., 1997), the

10

observation of episodic memory deficits in preclinical AD is not surprising. However, brain changes in preclinical AD are not limited to the medial temporal lobe. This is exemplified by the observations of increased rates of global brain atrophy before dementia onset (Fox & Schott, 2004; Fox, Warrington, & Rossor, 1999) and a general increase of white-matter hyperintensities (Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000). Thus, it is reasonable to expect impairment in cognitive domains besides episodic memory.

It is not known how long before an actual dementia diagnosis cognitive functioning starts being affected. Many studies have used follow-up intervals in the range of 2 to 3 years. However, a number of studies have observed cognitive deficits as long as 5 to 10 years before diagnosis (Amieva et al., 2005; Bäckman, Small, & Fratiglioni, 2001; Elias et al., 2000; Saxton et al., 2004; Small, Fratiglioni, Viitanen, Winblad, & Bäckman, 2000; Tierney, Yao, Kiss, & McDowell, 2005). Regarding the course of cognitive decline in preclinical dementia, some studies suggest that cognitive deficits remain stable up to approximately three years prior to diagnosis, when precipitous decline occurs (Amieva et al., 2005; Bäckman, Small, & Fratiglioni, 2001; Chen et al., 2001; Small et al., 2000). However, other studies have observed accelerated decline more than five years before a dementia diagnosis for episodic memory (Hall, Lipton, Sliwinski, & Stewart, 2000; Hall et al., 2001).

1.6 VASCULAR CAUSES OF COGNITIVE IMPAIRMENT

The prevalence of various vascular conditions increases in old age, with increasing mortality risk as a known consequence. Naturally, the presence of vascular disorders also increases the risk of VaD. However, vascular factors may affect cognition in many ways. In the past decade, the vascular contribution in AD has received a lot of attention. For example, a number of vascular conditions, including stroke (Honig et al., 2003), have been associated with an increased risk of AD (Breteler, 2000; Luchsinger et al., 2005). Furthermore, vascular lesions have been found to influence the clinical expression of AD. Neuropathological studies of AD have shown that the presence of vascular lesions contributes to the severity of cognitive impairment (Snowdon et al., 1997; Esiri, Nagy, Smith, Barnetson, & Smith, 1999; Riekse et al., 2004; Petrovitch et al., 2005). Relatedly, a recent neuroimaging study found the presence of white-matter lesions to be associated with poorer global cognitive functioning in early AD (Burns et al., 2005). Even in the absence of dementia, vascular conditions may influence cognitive performance. The presence of vascular risk factors at midlife has been shown to predict poor cognitive functioning in late life (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Kilander, Nyman, Boberg, & Lithell, 2000; Kivipelto et al., 2001; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995, Qiu, Winblad, & Fratiglioni, 2005). Furthermore, the presence of diabetes (Logroscino, Kang, & Grodstein, 2004; Yaffe et al., 2004), atherosclerotic disease (Breteler, Claus, Grobbee, & Hofman, 1994), and cardiovascular signs (Fahlander et al., 2000) has been associated with poorer cognitive functioning. In addition, cerebrovascular pathologies typically associated with VaD, such as stroke (Reitz, Luchsinger, Tang, Manly, & Mayeux, 2006), silent infarcts (Maeshima et al., 2002; Vermeer et al., 2003), and white-matter lesions (Breteler, van Amerongen et al., 1994; de Groot et al., 2000; Petkov et al., 2004; Skoog, Berg,

Johansson, Palmertz, & Andreasson, 1996) have been shown to influence cognition in normal aging.

Vascular disease is, thus, a common cause of cognitive impairment in old age. Another reason why the interest in vascular causes of cognitive impairment has increased in the last decade is that many vascular conditions are amenable to prevention. Preventive measures targeting persons with or at risk of having CVD might therefore result in great gains, such as prolonged life, postponement of dementia, and generally improved cognitive functioning. Recognizing that vascular disorders may influence cognitive functioning at different levels, a new concept has been proposed termed vascular cognitive impairment (VCI: Hachinski, 1994; Hachinski & Bowler, 1993). This label encompasses the whole spectrum of cognitive impairment, from the brain-at-risk stage through full-blown dementia. The use of the term VCI would put all cases where vascular causes could be assumed to contribute to the cognitive impairment into the same category, including AD with CVD. Current diagnostic criteria for VaD suffer from two major limitations (Bowler, Steenhuis, & Hachinski, 1999). The first is that they require substantial memory loss, which is not always present in patients with cognitive impairment caused by CVD. A second limitation is that a diagnosis of dementia requires cognitive impairment sufficient to affect normal daily activities, when treatment benefits would be largest at earlier stages of the dementia development.

Given that a number of vascular conditions have been associated with cognitive impairment, preclinical cognitive deficits might be expected also in VaD. The fact that VaD is a preventable disorder makes it even more important to shift the focus from the clinical to the preclinical phase. However, it is only quite recently that the preclinical period of VaD has started to receive some attention.

2 RESEARCH OBJECTIVES

The overall aim of this thesis was to address several unresolved issues regarding cognitive functioning for persons in a preclinical phase of dementia. Specifically, I sought to answer three main questions:

1) Do persons in a preclinical phase of VaD experience cognitive deficits in the years preceding a dementia diagnosis, similar to what has been observed in persons in a preclinical phase of AD?

2) Is cognitive performance and rate of cognitive change different for persons in a preclinical phase of dementia compared to persons in close proximity to death?

3) To what extent do preclinical dementia and impending death influence the magnitude of cross-sectional age-related cognitive deficits?

3 METHODS

3.1 THE KUNGSHOLMEN PROJECT

Data for this thesis were collected within the Kungsholmen Project (KP). The KP is a longitudinal, population-based study of the very old, with the general purpose of studying aging and dementia from medical, psychological, and sociological perspectives. A more detailed description of the project can be found elsewhere (Fratiglioni et al., 1991; Fratiglioni, Viitanen, Bäckman, Sandman, & Winblad, 1992). The original population comprised everyone living in the Kungsholmen parish of Stockholm, Sweden, October 1, 1987, who was born ≤1912 ($n = 2368$). Both people living at home or in institutions were included. By the year 2000, when the data collection was terminated, five waves of data collection had been completed, spaced approximately three years apart.

Dementia assessment at baseline was accomplished by means of a two-phase study design. Initially, all participants' cognitive status was assessed with the MMSE ($n = 1810$). This dementia screening phase also included a health interview, a social interview, and blood sampling. All persons scoring <24 on the MMSE at the screening phase were considered to have suspected dementia. They were invited back for a more detailed assessment, involving extensive medical, neurological, and psychiatric examinations, social and family interviews, laboratory blood analyses, and comprehensive cognitive testing. A total of 314 persons screening positive on the MMSE participated in this clinical phase together with a random sample scoring >23 on the MMSE ($n = 354$), matched on age and sex with the suspected dementia cases.

This thesis deals with the first four waves of the KP. For an overview of the number of participants and dropouts at baseline and the first three follow-ups, the reader may consult Figure 2. Those who died during the course of the project are included as participants in several of the studies and are therefore not regarded as drop-outs (except those who died before the baseline assessment). Of the original population of 2368 persons, 181 (8%) died before they could be examined at baseline. Persons who refused participation or had moved to a different area at the screening phase ($n = 377$; 16%) were not different from participants with regard to age and sex. Persons who participated in the screening phase but declined participation in the clinical phase ($n = 63$; 9%) were younger, included more men, and more frequently scored <24 on the MMSE relative to the examined subjects (Fratiglioni et al., 1991).

All persons participating in the screening phase at baseline were invited back for follow-up assessments. At these follow-up occasions, the comprehensive clinical protocol was re-administered, including a structured interview by a nurse, a medical examination by a physician, neuropsychological testing by a psychologist, and a structured interview with next-of-kin. For this thesis, only the dementia-free cohort identified at baseline is of interest ($n = 1475$). Persons from the dementia-free cohort who refused participation at first follow-up ($n = 168$; 12%) were younger, but had similar sex distribution and MMSE scores as the returning participants (Fratiglioni et

al., 1997). Very few of the nondemented individuals at first ($n = 45$; 6%) or second ($n = 32$; 7%) follow-up refused further participation.
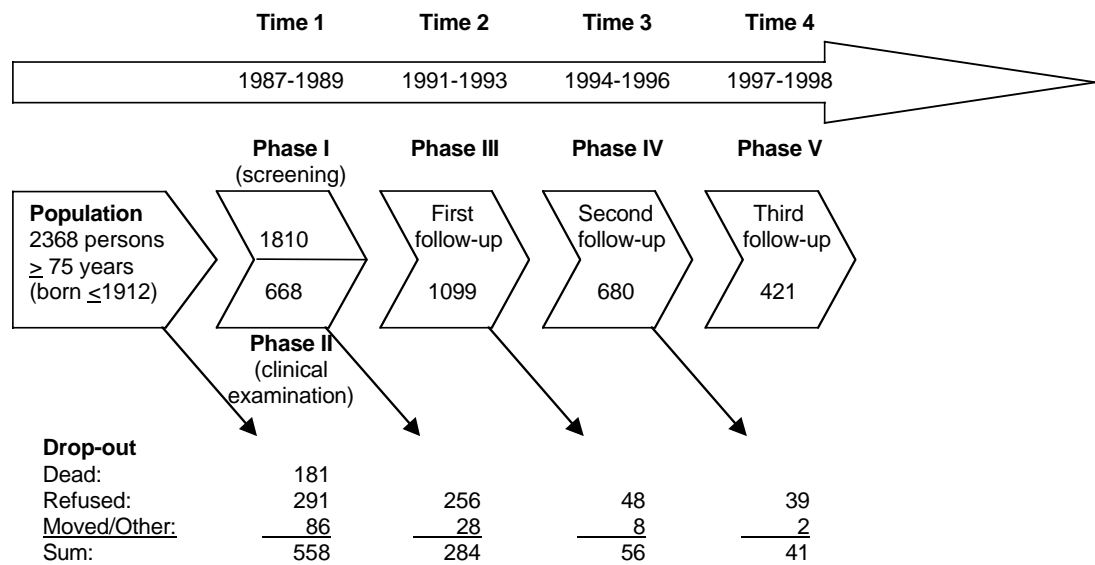

	Time 1	Time 2	Time 3	Time 4
	1987-1989	1991-1993	1994-1996	1997-1998

Figure 2. Number of participants and dropouts at baseline and first three follow-ups of the Kungsholmen Project (adopted from Study III).

3.2 DEMENTIA DIAGNOSIS

Diagnosis of dementia at baseline and follow-up visits were made according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised (DSM-III-R, American Psychiatric Association, 1987). At baseline, only the suspected dementia cases and the age- and sex-matched controls were assessed by a physician. The rest of the sample was classified as nondemented on the basis of their MMSE score.

The dementia diagnosis was made in three steps. First, the examining physician made a preliminary diagnosis. A second independent diagnosis was made based on computerized data by a physician external to the data collection. If there was agreement between the first and second diagnosis, this was considered the final diagnosis. In cases of disagreement, the final diagnosis was made by a supervising physician.

Following DSM-III-R guidelines, dysfunction of at least one cognitive function besides memory was required to receive a dementia diagnosis. The cognitive assessment used for diagnostic purposes included items regarding general knowledge and past personal information (memory), interpretation of proverbs (abstract thinking), problem solving (judgment), object naming (language), figure copying (visuospatial construction), and examination of simple motor activities (apraxia). The physicians were blind to the results of the cognitive test battery, which was administered at a separate occasion.

If memory impairment was evident but dysfunction of a second cognitive ability was questionable, the additional category "questionable dementia" was used. These persons were regarded as demented in this thesis.

15

For persons who died between assessments, their clinical records and death certificates were sought, and a dementia diagnosis was made based on this information. This was done in order to obtain the most complete information possible regarding the development of dementia. Death certificates were collected for everybody who died. For those who died and were nondemented at their last assessment, clinical records were available for 51%, whereas only hospital discharge diagnoses were available for 19%.

If a person was diagnosed with dementia at one of the follow-up assessments, the person was considered to be in a preclinical phase of dementia at the preceding testing occasions.

Differential diagnosis between AD and VaD was based solely on clinical data, as brain imaging or neuropathological examinations could not be performed in this large-scale population-based study. The AD diagnosis in the KP corresponds to the NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984), and the criteria used for VaD correspond to the NINDS-AIREN criteria for possible VaD (Roman et al., 1993). To support the clinical judgment, the Hachinski Ischemic Scale (HIS; Hachinski et al., 1975) was used. This scale has a maximum score of 18 and includes 13 items given different weights depending on how strongly they support a VaD diagnosis, such as abrupt onset (2), stepwise deterioration (1), fluctuating course (2), history of strokes (2), and evidence of associated atherosclerosis (1). A HIS score greater than 6 indicated VaD, a score of 5 or 6 indicated mixed dementia, and a score lower than 5 indicated AD. Both sensitivity and specificity of the HIS score have shown to be high (0.89) in differentiating between AD and VaD in pathologically verified cases (Moroney et al., 1997). A diagnosis of AD required gradual onset, progressive deterioration, and absence of all other specific causes of dementia. Mixed dementia cases were regarded as VaD cases in this thesis. The majority of VaD cases had a history of one or several clinically significant strokes related in time to the onset of dementia symptoms. Thus, the VaD diagnosis in the KP is mainly a diagnosis of post-stroke (strategic or multi-infarct) VaD.

3.3   COGNITIVE ASSESSMENT

In the KP, cognitive functioning was assessed in two different ways. All participants were administered the MMSE (Folstein et al., 1975), a measure of global cognitive ability. In addition to the MMSE, a comprehensive cognitive test battery was administered by a psychologist at a separate occasion. At baseline, only those participating in the clinical phase were assessed with the cognitive battery. Consequently, data on the cognitive battery is not available for all participants. In addition, some participants were not able to take part in the cognitive testing because of severe cognitive or physical impairment, or because they declined participation for various reasons. There are also missing data on specific tests due to fatigue or other difficulties in performing some of the tasks. In the studies included in this thesis, we have tried to benefit both from the bigger sample sizes available when using the MMSE as a measure of cognitive functioning, and from the more detailed information regarding specific cognitive domains available when using the smaller sample who completed the cognitive test battery. Table 1 shows the cognitive domains assessed in

16

the different empirical studies in this thesis. For a description of the tasks included, see the Introduction section.

Table 1. Cognitive variables examined in the five studies

Test	Cognitive domain	Source	Studies
MMSE	Global cognitive ability	Folstein et al. (1975)	II, III
Digit Span-forward	Primary memory	Wechsler (1981)	I, IV
Digit Span-backward	Primary memory Working memory	Wechsler (1981)	I
Free recall and recognition of random words	Episodic memory	Bäckman & Forsell (1994)	I, IV, V
Organized recall	Episodic memory	Bäckman & Forsell (1994)	I, V
Face recognition	Episodic memory	Bäckman & Forsell (1994)	I, V
Block Design	Visuospatial ability	Wechsler (1981)	I, IV, V
Clock reading	Visuospatial ability	Christensen (1984)	I
Clock setting	Visuospatial ability	Christensen (1984)	I, V
Letter fluency	Verbal ability	Lezak (1995)	I, V
Category fluency	Verbal ability	Lezak (1995)	I, IV, V

3.4   BACKGROUND VARIABLES

Many of the background variables used in the different studies, including level of education and subjective memory complaints, were derived from the structured interview and clinical examination in the KP. Psychiatric diseases were diagnosed according to DSM-III-R criteria (American Psychiatric Association, 1987) at baseline and according to DSM-IV criteria (American Psychiatric Association, 1994) at subsequent examinations. Functional status was assessed with the Katz index of activities of daily living (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963). It includes questions about whether the subject is dependent in feeding, continence, transferring, going to the toilet, dressing, and bathing. Apolipoprotein E (APOE) genotype was determined for all subjects where blood samples were available ($n = 1235$). DNA was extracted from peripheral white blood cells and APOE allelic status was determined using standard methods (Basun et al., 1996).

Data on birth and death dates were derived from the official register and is thus exact information. Information about a history of vascular disease (e.g., heart disease, CVD) and malignancies were derived from the computerized Stockholm inpatient register, including admission and discharge diagnoses from all occasions where Stockholm city

residents received hospital care from April 1969 and onwards. Both the main diagnosis and up to five additional diagnoses were included.

3.5 STATISTICAL ANALYSES

Analyses of variance (ANOVAs) and chi-square tests were used to examine differences among groups regarding baseline characteristics in all studies.

Univariate and multivariate ANOVAs were used to examine differences in cognitive functioning among groups (Study I, II, V). In Study II, we also used repeated-measures ANOVAs together with paired t-tests to determine the presence of cognitive decline. Age, sex, and education were used as covariates.

Logistic regression analyses were used to examine the strength of the association between cognitive test performance and future dementia status (Study I, II), covarying for age, sex, and education.

In Study III and IV, we used multilevel modeling (Bryk & Raudenbush, 1992) to compare initial cognitive status and rate of cognitive change among groups. We employed a full maximum likelihood approach and included only variables that significantly improved model fit, as indicated by a lower deviance score (Singer & Willett, 2003). Multilevel modeling affords several advantages compared to conventional approaches for the analysis of change (e.g., repeated-measures ANOVA). For example, it allows simultaneous assessment of within-person change (Level 1) and between-person differences in within-person change (Level 2). Another advantage is that this method efficiently deals with missing data and is able to use all available information. This is an important factor in longitudinal studies where data might be missing for one or several occasions. Specifically, more accurate estimates are obtained relative to analytic methods that employ list-wise deletion, as individuals with incomplete data may be systematically different (e.g., in poorer health) relative to those with complete data. Further, multilevel modeling does not require equal spacing between assessments across individuals (which is uncommon in longitudinal studies). Instead, the differences in follow-up intervals are included in the analyses and actually improve the precision of within-person slope estimates. The end result is an estimation of aggregate change (fixed effects) and individual deviation about this average (random effects). In Study III, only age and education were used as covariates, as sex did not significantly improve model fit. For Study IV, age, sex, and education were always statistically controlled in order to facilitate comparisons across models.

Hierarchical regression analyses were used in Study V to determine the amount of variance in cognitive performance that was accounted for by age in our different groups. Sex and education were used as covariates.

3.6 ETHICAL CONSIDERATIONS

All waves of the KP have been approved by the ethical committee of Karolinska Institutet, Stockholm, Sweden. Informed consent was derived from all participants, or, if the participant's cognitive functioning was severely impaired, from next-of-kin.

4 RESULTS

Table 2 shows number of participants and baseline characteristics of the different groups examined in the five studies included in this thesis.

Table 2. Baseline characteristics across study samples

Study	*n*	% female	Mean age (years)	Mean years of education/ % with <8 years
Study I				
Incident VaD	15	80%	85	8
Incident AD	43	95%	84	8
Control group	149	81%	84	9
Study II				
Incident VaD	22	73%	82	9
Control group	455	77%	79	10
Study III				
Impending death	534	67%	83	49%
Preclinical dementia	417	82%	82	57%
Control group	249	81%	80	41%
Study IV				
Impending death	187	69%	84	51%
Preclinical dementia	173	87%	83	58%
Control group	225	80%	80	39%
Study V				
Impending death	69	75%	87	8
Preclinical dementia	61	95%	85	8
Remaining sample	207	80%	83	9

4.1 STUDY I

Numerous studies have demonstrated the existence of a preclinical period in AD during which cognitive deficits are detectable. The aim of Study I was to determine whether preclinical cognitive deficits are also present in VaD. A second aim was to investigate

whether the pattern of cognitive deficits in preclinical VaD is similar to that observed in preclinical AD.

The sample consisted of persons from the dementia-free cohort who had completed the cognitive test battery either at baseline or first follow-up of the KP. To increase the statistical power, we used incident dementia cases from both first and second follow-up. Thus, Time 1 was either baseline or first follow-up of the KP, depending on whether time of diagnosis was first or second follow-up. In order to match these incident dementia cases to controls in terms of age and potential practice effects on the cognitive tests, the controls were randomly assigned a Time 1 measurement point. Specifically, an equal proportion of controls and dementia cases were selected to have baseline or first follow-up as their Time 1 assessment. The follow-up interval was approximately 3 years for all individuals. The sample was screened for major depression, dysthymia, psychosis, and Parkinson's disease at Time 1. We compared cognitive performance at Time 1 for those who were diagnosed with either VaD or AD at Time 2 and those who remained nondemented during the follow-up period.

The general pattern indicated poorer cognitive performance for both incident dementia groups compared to the controls (see Figure 3). The incident VaD group performed at a lower level compared to the controls on three out of four episodic memory measures: random recall, word recognition, and face recognition. The incident AD group performed worse than the controls on all measures of episodic memory, and also on the verbal fluency and visuospatial measures, except for clock reading. Neither of the incident dementia groups showed deficits on the Digit Span tasks.

No reliable differences were observed on any cognitive measure between the incident VaD and AD groups in the overall analysis. Furthermore, no significant differences were found ($ps > 0.10$) when contrasting these groups on the cognitive tasks with separate t-tests, thereby decreasing the risk of committing type II errors.

In the logistic regression analyses, face recognition was the only measure that showed an independent association with incident VaD three years later. Face recognition also showed the strongest association with future AD. However, also Block Design and word recognition were independently associated with incident AD, again indicating more pronounced cognitive deficits in preclinical AD.

Main findings: The results from this study show that preclinical cognitive deficits may be detected three years before a diagnosis of VaD, suggesting that vascular pathology affects cognitive functioning before the occurrence of a stroke leading to clinical VaD. Furthermore, the pattern of cognitive deficits in preclinical VaD was found to be similar to that observed in preclinical AD, with the most prominent deficits being observed for the episodic memory domain.
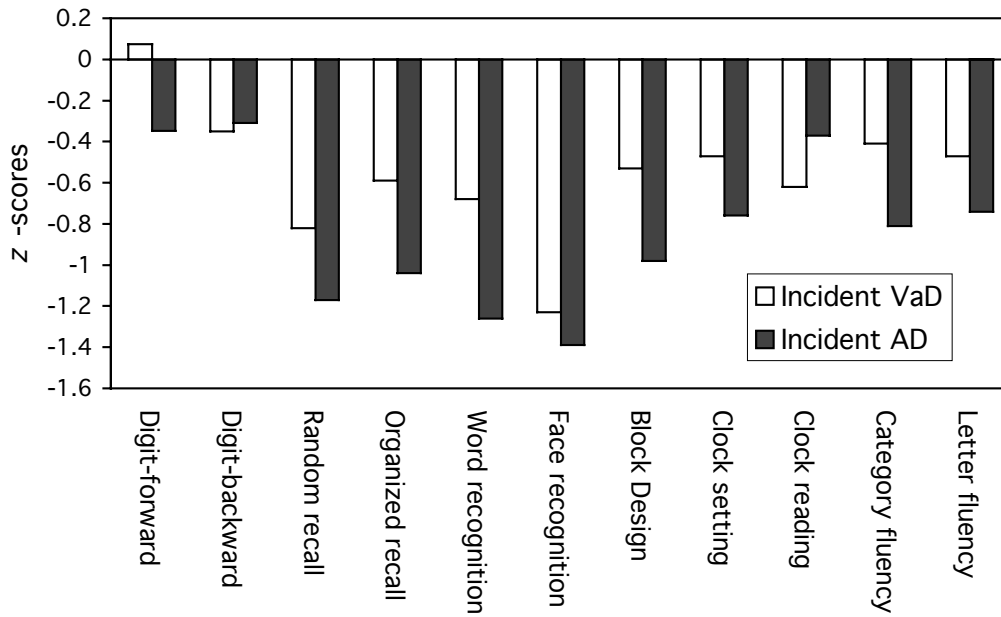
Figure 3. Results on the cognitive tests at Time 1 expressed in *z*-scores for incident VaD and AD persons relative to the reference group (control means set at 0; adopted from Study I).

4.2 STUDY II

Previous studies have provided evidence of a long preclinical phase in AD. In Study I, we were able to demonstrate preclinical cognitive deficits three years before a diagnosis of VaD. The purpose of Study II was to extend these findings by examining whether cognitive deficits are present already six years before a diagnosis of VaD.

All participants in this study were nondemented at baseline and first follow-up assessment of the KP. The sample consisted of those persons who were either diagnosed with VaD (the incident VaD group) or remained alive and nondemented (the control group) at second follow-up. The sample was screened for psychosis and Parkinson's disease.

Results showed that although the incident VaD group performed at a lower level on the MMSE compared to the controls six years before diagnosis, there were no significant differences between the two groups. However, three years before diagnosis, the incident VaD persons performed at a significantly lower level on the MMSE relative to the controls. Consistent with this pattern of results, the incident VaD persons declined significantly on the MMSE between baseline and first follow-up. As expected, they also showed significant cognitive decline between first follow-up and time of diagnosis. The individual MMSE subscales that showed significant impairment three years before diagnosis were orientation to time and place, delayed recall, and attention. In view of the findings from Study I, it is noteworthy that the first three subscales all have an episodic memory referent, whereas performance on the attention subscale reflects working memory abilities. In a logistic regression analysis, the association between

cognitive performance and incident VaD remained even after controlling for demographic factors and a history of vascular disorders.

Main findings: The results of this study confirm previous findings that poor cognitive performance may be an indicator of prodromal VaD. They also suggest that cognitive testing could constitute a valuable element of the clinical examination when trying to identify persons at risk of developing VaD.

4.3   STUDY III

Although both impending death and preclinical dementia are associated with cognitive impairment in old age, the effect of these two outcomes on cognitive performance has rarely been examined within the same study. In Study III, we compared initial level and rate of cognitive change for three groups: persons in close proximity to death, persons in a preclinical phase of dementia, and persons who remained alive and nondemented throughout the study.

All participants were nondemented at baseline. The impending death group consisted of persons who were nondemented during their entire follow-up period and died between baseline and third follow-up. Thus, this group was free of persons with preclinical dementia. The preclinical dementia group consisted of persons who were diagnosed with dementia at one of the three follow-up assessments, and the control group comprised persons who remained alive and nondemented during the entire assessment period. The sample was screened for psychosis and Parkinson's disease. The participants were assessed with the MMSE a maximum of three times over an 11-year period. For the preclinical dementia group, only cognitive information for the assessment points prior to the time of diagnosis was used. In order to equate the time frame for the collection of cognitive data across groups, only data up to the second follow-up was used for the controls.

Change in MMSE performance was modeled as a function of years to event. The event for the impending death group was the exact death date. For the preclinical dementia group, the event was the date when the diagnostic criteria for dementia were fulfilled. Given the three-year retest interval, this was estimated to be the midpoint between the last nondemented assessment and the follow-up occasion when they were diagnosed with dementia. The event for the controls was defined as occurring at the midpoint between the second and third follow-up testing.

Results for the total sample showed significant effects of both impending death and preclinical dementia at intercept (three years before event), with the preclinical dementia group showing the poorest performance. In addition, the preclinical dementia group declined twice as fast on the MMSE relative to the other groups. However, no accelerated decline was observed for the impending death group after persons with preclinical dementia had been excluded (see Figure 4). The same pattern of results was observed when the sample was split into an old-old (75 to 80 years) and an oldest-old (81+ years) age group, although group differences were attenuated for the oldest-old group.

22

Previous studies on impending death do not typically control for the effect of preclinical dementia. In an additional set of analyses, we investigated the influence of preclinical dementia on the magnitude of terminal-decline effects. When contrasting the control group with all persons who died during the follow-up period (including those with preclinical dementia), we observed an effect size ($d = 0.70$) intermediate to that observed for the contrast between the controls and the impending death group ($d = 0.50$) and the controls and the preclinical dementia group ($d = 0.90$). In all cases, the controls showed the highest cognitive performance.
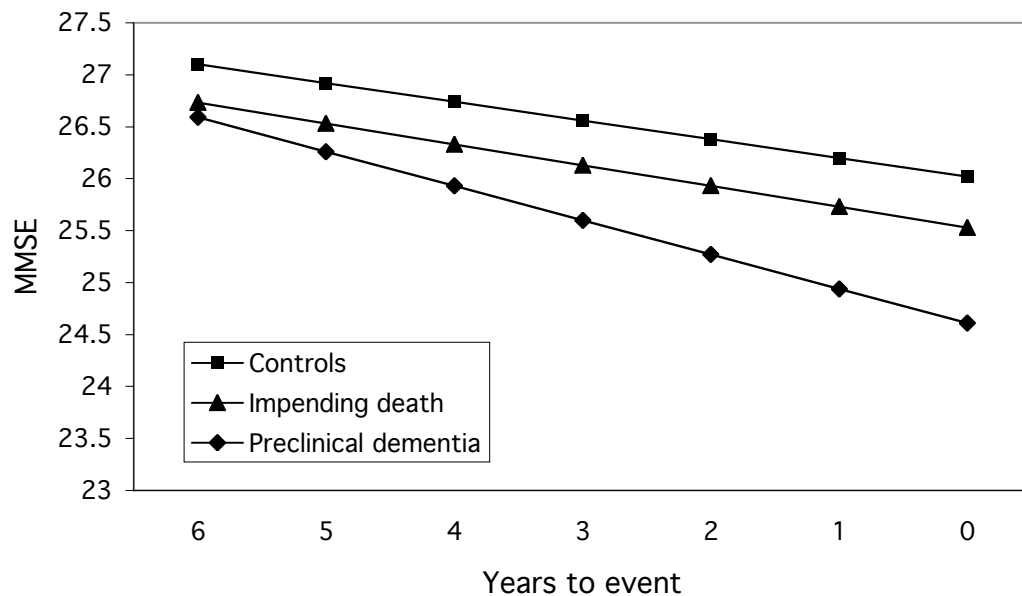

Figure 4. Average Mini-Mental State Examination change as a function of years to event for the control, impending death, and preclinical dementia groups (adapted from Study III). All effects are adjusted for age and education.

Main findings: The results of this study show that, although both the impending death and the preclinical dementia groups had poorer initial cognitive performance, only the persons with preclinical dementia exhibited accelerated cognitive decline relative to the controls. The lack of accelerated decline in proximity to death after excluding persons with dementia or preclinical dementia suggests that part of the terminal-decline effect demonstrated in previous investigations may reflect preclinical dementia deficits. Further, given that impending-death effects were observed at intercept, accelerated cognitive decline might be a more reliable indicator of preclinical dementia than a low cognitive score due to confounds associated with cross-sectional cognitive performance.

4.4 STUDY IV

In Study III, we demonstrated that a sizeable proportion of the impending-death effect on cognition was due to the impact of preclinical dementia. We observed no

accelerated decline on the MMSE in proximity to death after persons with preclinical dementia had been excluded. However, the MMSE is a relatively crude measure of cognitive functioning. Thus, the aim of study IV was to explore possible terminal-decline effects on multiple cognitive tasks after controlling for the effect of preclinical dementia.

We used the same methodological approach as in Study III. Initial level and rate of cognitive change were compared for three groups: persons in close proximity to death, persons in a preclinical phase of dementia, and persons who remained alive and nondemented throughout the study. However, as not everyone had data on the cognitive test battery, the sample size was considerably smaller compared to Study III. The sample consisted of persons from the dementia-free cohort who had participated in the cognitive testing at least once, and who either remained nondemented through all three follow-ups, or were diagnosed with dementia or died during the follow-up period. The sample was screened for psychosis and Parkinson's disease. The cognitive tasks were selected to vary in the degree of normal age-related decline, with some tasks yielding robust age-related decline (i.e., word recall, Block Design), whereas others typically exhibit reduced or nonexistent age-related change (i.e., word recognition, Digit Span-forward, category fluency).

The results showed similar patterns at intercept as in Study III, with significant effects of both impending death and preclinical dementia on all cognitive tasks. The preclinical dementia group performed at a lower level compared to the impending death group on all tasks except Digit Span-forward. Contrasting the control group with all persons who died during the follow-up period (including those with preclinical dementia) again led to a considerable increase of the effect of impending death on cognitive performance.

Regarding rate of change, the controls showed reliable decline on free recall of random words and Block Design, the most executively demanding of the tasks included. In contrast to Study III, significant terminal-decline effects were observed. The impending death group declined at a faster rate compared to the controls on Digit Span-forward, word recognition, and category fluency. Notably, these were the tasks where no reliable decline was observed for the controls. The preclinical dementia group declined at a faster rate compared to the controls on all tasks, and faster than the impending death group on word recognition and Block Design.

Main findings: The results of this study provide further support for the finding that the effect of impending death on cognition is largely mediated by preclinical dementia. However, terminal decline was observed for select cognitive tasks even after controlling for preclinical dementia, supporting previous suggestions that terminal cognitive decline is a multi-determined phenomenon. The finding that the tasks that showed no age-related decline for the controls were most sensitive for detecting terminal-decline effects is consistent with the view that tasks that are generally not affected by normal aging are most suitable for detecting terminal-decline effects.

4.5 STUDY V

The presence of preclinical dementia cases in samples of very old adults may underestimate the mean and overestimate the variability in cognitive performance at a given time point. However, does the presence of preclinical dementia cases also affect our possibility to draw sound conclusions regarding the association between age and cognitive performance in cross-sectional studies? A study by Sliwinski, Lipton, Buschke, and Stewart (1996) indicates that this may be the case. They investigated the influence of preclinical dementia on the age-cognition relationship in a volunteer sample of 75- to 85-year olds. The key finding was that eliminating persons who had developed dementia (or died) at follow-up reduced the size of the age-related deficits. Study V constituted an extension of the Sliwinski et al. study in that we (a) examined the effect of preclinical dementia and impending death in separate analyses, and (b) used a population-based as opposed to a volunteer sample. As the probability of dying as well as developing dementia increases in late life, also the inclusion of individuals in close proximity to death could lead to an overestimation of the magnitude of normal age-related differences. Thus, the aim was to examine the influence of preclinical dementia and impending death on the cross-sectional relationship between age and cognitive performance in a population-based sample of persons ≥75 years.

The sample consisted of those nondemented persons who participated in the cognitive testing at baseline. The sample was screened for depression, dysthymia, and psychosis. In addition, participants who failed to return for the follow-up examination for reasons other than death were excluded. The original sample was divided into subgroups on the basis of the participants' follow-up status, 3 years after baseline assessment. Those persons who died between baseline and first follow-up were included in the impending death group, and those diagnosed with dementia were included in the preclinical dementia group. The remaining sample comprised those persons who were still alive and nondemented at follow-up.

All cognitive measures in the KP test battery that correlated negatively with age (rs > 0.20, ps < 0.10) were included in this study. The tasks were measures of visuospatial ability (Block Design, clock setting), verbal fluency (category and letter fluency), and episodic memory (free recall and recognition of random words, organized recall, and face recognition).

The amount of variance accounted for by age in the different samples was determined by means of hierarchical regression analyses. Separate analyses were performed for the original and remaining samples, as well as for the remaining plus preclinical dementia samples and the remaining plus impending death samples. Results showed that removal of the preclinical dementia and the impending death groups from the original sample had a relatively small effect on the age-related cognitive variation. Yet, for category fluency, letter fluency, and word recognition, the age-related variation dropped to a level where it was no longer significant in the remaining sample. However, the size of the age effect for these variables was relatively small even in the original sample. Furthermore, the reverse pattern, with an increase of the age-related variation in the remaining sample, was observed for face recognition. When adding the impending death and preclinical dementia groups separately to the remaining sample, we found

that removal of the impending death group had a somewhat larger impact on the age-cognition relationship. Examination of interaction effects showed that the negative effect of age on cognitive performance was similar across samples.

Main findings: Although removal of persons in close proximity to death or in a preclinical phase of dementia clearly affects an elderly sample's mean cognitive performance, the cross-sectional age-cognition relations remain relatively unchanged. These results suggest that biological aging processes, besides those directly related to dementia or death, may have negative effects on cognitive functioning in the elderly.

5 DISCUSSION

5.1 COGNITIVE FUNCTIONING IN PRECLINICAL VAD

Results from both Study I and II show that preclinical cognitive deficits are indeed present in the years preceding a diagnosis of VaD. This finding is consistent with previous observations that a number of vascular conditions may exert negative influences on cognitive performance. These include diabetes (Logroscino et al., 2004; Yaffe et al., 2004), atherosclerotic disease (Breteler, Claus, et al., 1994), and hypertension (Elias et al., 1993; Kilander et al., 2000; Kivipelto et al., 2001; Launer et al., 1995, Qiu et al., 2005) – all important risk factors for stroke (Warlow, 2003). Pathologies typically associated with VaD, such as silent strokes and white-matter lesions, have also been associated with an increased risk of future stroke (Bernick et al., 2001; Wong et al., 2002), as well as with impaired cognitive functioning in persons free of dementia (Breteler, van Amerongen, et al., 1994; de Groot et al., 2000; Maeshima et al., 2002; Petkov et al., 2004; Skoog et al., 1996; Vermeer et al., 2003). The prevalence of these conditions should be high in a sample of persons with impending VaD, making it reasonable to expect preclinical cognitive deficits in VaD.

The second main finding from Study I and II is that the pattern of cognitive deficits in preclinical VaD was similar to that observed for preclinical AD. The fact that no significant differences were observed between the two preclinical dementia groups is in line with the results of a number of previous investigations showing similar levels of cognitive impairment for early clinical VaD and AD for a range of cognitive domains (Almkvist, Bäckman, Basun, & Wahlund, 1993; Almkvist, Fratiglioni, Agüero-Torres, Viitanen, & Bäckman, 1999; Erker, Searight, & Peterson, 1995; Erkinjuntti, Laaksonen, Sulkava, Syrjäläinen, & Palo, 1986; Fahlander, Wahlin, Almkvist, & Bäckman, 2002; Hassing & Bäckman, 1997). Although the results point at a somewhat more pronounced cognitive deficit in preclinical AD, with this group being impaired on a broader range of cognitive domains, an important finding is that both dementia disorders showed the largest impairment for episodic memory three years before diagnosis. Other recent findings concerning preclinical VaD support the notion that episodic memory impairment, which is considered to be a cardinal feature of AD, is present prior to a diagnosis of VaD. For example, Sacuiu, Sjögren, Johansson, Gustafson, and Skoog (2005) found episodic memory impairment to be predictive of incident VaD and incident AD alike. Similarly, poor episodic memory performance was associated with incident dementia in a group classified with vascular cognitive impairment (Ingles, Wentzel, Fisk, & Rockwood, 2002).

Six years before diagnosis, we observed no significant difference between the incident VaD persons and the controls with regard to cognitive performance, although previous studies have demonstrated cognitive deficits five to ten years before a diagnosis of preclinical AD (Amieva et al., 2005; Bäckman, Small, & Fratiglioni, 2001; Elias et al., 2000; Saxton et al., 2004; Small et al., 2000; Tierney et al., 2005). This might be due to power problems as the number of preclinical VaD persons in our study was relatively small. However, it may also reflect earlier occurrence of cognitive deficits in AD compared to VaD.

Not long ago, there were almost no studies concerning cognitive functioning in preclinical VaD. However, during the past few years, a number of studies have been published on this topic. For example, Meyer and colleagues reported that cognitively impaired persons about to develop VaD showed lower performance and faster decline on the MMSE compared to persons with stable cognitive impairment (Meyer, Xu, Thornby, Chowdhury, & Quach, 2002a; 2002b). Interestingly, two years before diagnosis, there were no significant differences on the MMSE total score, or on the subscales, between preclinical VaD and preclinical AD (Meyer at al., 2002a). Relatedly, we observed similar levels of cognitive deficits for preclinical VaD and AD on the MMSE three years before diagnosis, with a measure of episodic memory (delayed recall) being the best predictor of both incident VaD and incident AD (Jones, Laukka, Small, Fratiglioni, & Bäckman, 2004). An exception to the findings of similar levels of cognitive impairment was observed in a study comparing the effect of preclinical dementia on two verbal fluency tasks. Although both incident dementia groups showed poorer cognitive performance on letter fluency, the incident VaD persons outperformed the incident AD group on category fluency three years before diagnosis (Jones, Laukka, & Bäckman, 2006). To summarize, there is now substantial evidence that a preclinical phase with cognitive deficits is present in VaD, the pattern of cognitive deficits being largely similar to that observed in preclinical AD.

Although many investigations show similar levels of cognitive impairment for preclinical and early clinical VaD and AD, the results from a number of studies suggest that executive functioning may be selectively impaired in VaD (Looi & Sachdev, 1999). The executive dysfunction seems to be especially pronounced in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL: Buffon et al., 2006; Charlton, Morris, Nitkunan, & Markus, 2006), and other forms of subcortical ischaemic vascular disease (Jokinen et al., 2006; Kramer, Reed, Mungas, Weiner, & Chui, 2002). CADASIL is a genetic form of small-vessel disease that is considered to provide a model for pure VaD. In a recent study, cognitive deficits were observed in a very early phase of the disease, before a transient ischemic attack or stroke had occurred. In contrast to preclinical AD, working memory and executive function were most impaired, whereas episodic memory functioning was relatively well preserved late in the disease (Amberla et al., 2004). Thus, which cognitive domain is most affected might depend on which subtype of VaD is investigated. In this thesis, however, we were restricted to examining persons with post-stroke VaD.

Similar to the notion that executive functioning should be selectively impaired in VaD, several studies have observed comparatively larger episodic memory deficits in AD (Looi & Sachdev, 1999). Regardless of whether one cognitive domain is more impaired in one of the dementia types or not, the cognitive deficit for either AD or VaD is not limited to a single type of task. For example, a meta-analysis on cognitive functioning in preclinical AD demonstrated similar levels of impairment in executive functioning and episodic memory (Bäckman et al., 2005). The relationship between brain changes and behavioral outcome is complex, making it possible for the same underlying pathology to cause impairment in more than one cognitive domain. Similarly, different types of brain pathologies may cause the same type of cognitive impairment. For

example, episodic remembering draws on a large distributed network (Cabeza & Nyberg, 2000) involving, besides the hippocampus, frontostriatal circuitry that is important for executive functioning. Alterations at any location in this network may cause episodic memory impairment. A study comparing AD and subcortical stroke observed a double dissociation between memory dysfunction and regional glucose metabolic activity. Whereas performance on an episodic memory task correlated with left hippocampal and temporal lobe metabolism in AD patients, it correlated with prefrontal lobe metabolism in patients with subcortical stroke (Reed, Eberling, Mungas, Weiner, & Jagust, 2000). Thus, the same cognitive deficit may have different neurological underpinnings depending on the etiology of the dementia disorder.

In this thesis, we observed preclinical cognitive deficits in VaD three years before diagnosis. This finding is biologically plausible given that persons with VaD may be exposed to vascular risk factors many years before diagnosis and several vascular risk factors have been associated with impaired cognitive functioning. However, it cannot be excluded that the VaD persons were also affected by degenerative processes characteristic of AD, as overlap in brain pathology between the two dementia disorders is common (Barker et al., 2002; Kalaria & Ballard, 1999). Further, such overlap becomes increasingly likely with increasing age, as age is a major risk factor for both dementia disorders. The overlap in dementia pathology might obscure potential differences in cognitive functioning between preclinical VaD and preclinical AD. As we did not have access to neuroimaging or neuropathological data, we do not know how much AD pathology was present in persons with preclinical VaD, or to what extent cerebrovascular pathology could be observed in persons with preclinical AD.

Another issue that might complicate the identification of possible differences in cognitive performance between VaD and AD concerns the diagnostic criteria for VaD (Bowler et al., 1999). Instead of using diagnostic criteria specifically designed to identify persons with VaD, receiving a VaD diagnosis first requires a diagnosis of dementia. The diagnostic criteria for dementia are mainly based on the clinical features of AD and require memory loss and level of cognitive impairment sufficient to affect normal daily activities. These criteria are not well suited for VaD, as executive functions might be at least equally impaired as episodic memory. This results in a diagnostic bias where persons with executive dysfunction, without prominent memory loss, may not be recognized as demented (Bowler et al., 1999).

Concluding summary: Cognitive deficits are observed at least 3 years before a diagnosis of VaD. This observation is consistent with previously established negative associations between cognitive performance and a number of vascular conditions likely present in preclinical VaD. Further, at least for post-stroke VaD, the pattern of preclinical cognitive deficits largely resembles that observed for AD. Thus, previous findings of similar cognitive deficits in the early clinical phases of VaD and AD can be extended to the preclinical phases of these diseases.

5.2 THE EFFECT OF PRECLINICAL DEMENTIA VS. IMPENDING DEATH ON COGNITIVE PERFORMANCE

In Study III and IV, we were able to demonstrate that the effect of impending death on cognitive functioning in old age is largely mediated by preclinical dementia. Excluding persons with preclinical dementia from the impending death group resulted in clearly attenuated effects of impending death on cognitive performance. However, there were still significant effects of impending death at cross-section. In addition, the impending death group showed a faster rate of decline compared to the controls on select cognitive tasks even after excluding persons with preclinical dementia.

The biological underpinnings of mortality-related cognitive deficits have long remained unknown. It has been hypothesized that either the influence of specific diseases or a more general biological systems breakdown, resulting in decreased biological vitality, causes the effect (Bäckman & MacDonald, 2006; Berg, 1996; Small & Bäckman, 1999). It could also be that these two factors work in combination. Findings from this thesis suggest that dementia is one important disease contributing to the cognitive deficits observed in close proximity to death, perhaps even the most important. Given that (a) dementia and mortality risks both increase exponentially with age, and (b) preclinical cognitive deficits can be observed several years before a diagnosis of dementia can be rendered, a large proportion of elderly persons close to death might be affected by preclinical dementia. Differences in exclusion criteria regarding preclinical dementia cases could account for some discrepancies in results from previous investigations on terminal-decline effects, as many studies have not controlled for preclinical dementia.

Even though the effect of impending death was clearly attenuated after the removal of the preclinical dementia persons, significant impending-death effects were still observed at intercept for all cognitive tasks. Thus, both impending death and preclinical dementia were associated with cross-sectional cognitive deficits for a range of cognitive domains. However, whereas significant terminal-decline effects support an association between cognitive performance and time to death, impaired cognition at cross-section might reflect multiple factors. For example, the person might have a life-long history of below-average cognitive performance. Previous studies have shown that childhood mental ability predicts age at death (Kuh, Richards, Hardy, Butterworth, & Wadsworth, 2004; Whalley & Deary, 2001). Another possibility is that some persons in the impending death group were in a preclinical phase of dementia, although they died before they could be diagnosed. Acute illness during the last months of life might also have influenced baseline cognitive performance.

Although a global cognitive impairment was observed for both the impending death and preclinical dementia groups at cross-section, the findings regarding patterns of change were less consistent. The preclinical dementia group, on the one hand, declined at a faster rate compared to the controls on all tasks. The impending death group, on the other hand, declined at the same rate as the controls on the MMSE (Study III), whereas significant terminal-decline effects were observed for select cognitive tasks in Study IV. This pattern was seen after controlling for preclinical dementia. In this context it should be noted that, although a large number of conditions have been associated with

poorer cognitive performance at cross-section, few factors have been shown to influence cognitive change. Dementia-related pathology, however, constitutes a major exception to this rule. Similar to our findings, a recent study on the effect of depressive symptoms on cognitive performance observed minimal cognitive decline over time for a group of persons who remained dementia free, whereas the eventual-dementia group showed marked cognitive decline. Thus, despite significant associations with baseline cognitive performance, depressive symptoms were not associated with subsequent cognitive decline. The authors concluded that substantial cognitive decline over time likely reflects incipient dementia (Ganguli, Du, Dodge, Ratcliff, & Chang, 2006).

AD is characterized by progressive brain deterioration accompanied by cognitive decline. Given the long preclinical phase of AD, pathological brain changes might influence cognitive functioning many years before a dementia diagnosis. Toward this end, AD pathology has been related to subtle episodic memory deficits even for persons without cognitive impairment (Bennett et al., 2006). Further, greater annual rate of shrinkage in the enthorhinal cortex has been associated with cognitive decline in healthy elderly persons (Rodrigue & Raz, 2004). In relation to VaD, progressive vascular disease has been associated with accelerated cognitive decline. For example, in the Rotterdam Scan Study, the presence of silent brain infarcts at baseline was associated with worse cognitive performance, whereas decline in cognitive functioning was restricted to those with additional silent infarcts (Vermeer et al., 2003). Relatedly, Comijs, Dik, Deeg, and Jonker (2004) showed that an increase of cardiovascular diseases at follow-up predicted further cognitive deterioration. Thus, findings from a number of studies suggest that, although many factors may influence cognitive performance at a given time point, accelerated cognitive decline is a sign of impending dementia.

Although controlling for preclinical dementia eliminated a substantial proportion of the terminal-decline effect, terminal decline was still present for some tasks in Study IV. In comparison to the controls, the impending death persons showed significantly faster decline for Digit Span-forward, recognition of random words, and category fluency. Notably, accelerated decline was observed only for those tasks where the controls' performance remained stable over time. This pattern of results supports previous notions that tasks that are more resistant to age-related change should be more sensitive to terminal-decline effects (White & Cunningham, 1988; Small & Bäckman, 1999). Little or no cognitive decline in the control group clearly leaves comparatively more room for deterioration in the impending death group. In line with this reasoning, the obtained results suggest that level of task difficulty may be more important for the likelihood of observing terminal decline than the cognitive domain assessed. For example, terminal decline was observed for recognition, the more supported episodic memory task, but not for free recall that even the controls may find cognitively demanding.

Among other things, the findings from these studies highlight the complexity of the relationship between aging and cognition, making it a difficult task to determine the influence of any single factor on cognitive functioning. Clearly, preclinical dementia explained a substantial proportion of the effect of impending death on cognition. However, terminal decline was observed even after controlling for preclinical dementia.

In addition, marked rates of cognitive decline were observed for the control group, suggesting the effect of cumulative aging processes. In particular, the oldest-old controls declined at a fast rate. This may reflect the fact that these controls were relatively closer to dementia or death compared to their younger counterparts. Consequently, attenuated effects of impending death and preclinical dementia were observed in the oldest age group.

Concluding summary: Controlling for preclinical dementia leads to markedly attenuated effects of impending death on cognition. Thus, part of the terminal-decline effect demonstrated in previous investigations likely reflects preclinical dementia deficits. However, preclinical dementia does not explain the entire effect, as terminal decline can still be observed for tasks showing little age-related change.

5.3 THE INFLUENCE OF PRECLINICAL DEMENTIA AND IMPENDING DEATH ON THE MAGNITUDE OF CROSS-SECTIONAL AGE-RELATED COGNITIVE DEFICITS

In Study V, consistent with expectations, we found that removal of the preclinical dementia and impending death persons from the original sample resulted in higher means for all cognitive tasks. However, the main finding from this study was that the removal of the preclinical dementia and impending death groups had little influence on the cross-sectional relationship between age and cognitive performance.

The tasks where the association between age and cognition dropped below conventional significance in the remaining sample were category and letter fluency and word recognition. However, the age effect was reduced only slightly and the association with age for these variables was relatively weak even for the original sample. In addition, an even greater change of the age effect, but in the opposite direction, was observed for face recognition. Examination of interaction effects revealed similar age-cognition associations in the preclinical dementia and impending death groups as in the remaining sample. Thus, the negative effects of age on cognition generalized across samples.

When comparing the effects of removing the preclinical dementia group and the impending death group from the original sample, it seemed that removal of the impending death group resulted in as great, or even greater, reductions of the age effect. In part, this might be due to the age difference being larger between the impending death group and the original sample than between the preclinical dementia group and the original sample. This should make the room for influencing the age-cognition relationship comparatively larger for the impending death group.

The results of Study V show that preclinical dementia and impending death do not explain all of the cognitive decline that we experience in late life. This confirms the findings from Study III and IV, where even the controls showed considerable cognitive decline. Primary aging processes might explain part of the age-related differences that remain after the removal of persons in a preclinical phase of dementia or in close proximity to death from the original sample. Losses in cognitively relevant brain structures and neurotransmitters have been observed with advancing age, with an onset

of the reduction already in young adulthood (Bäckman, Ginovart, et al., 2000; Raz, 2000; Volkow et al., 1998). However, the association between age and cognitive performance was not very strong for any of the tasks even in the original sample. This may be explained by the relatively narrow age span in this sample (75-96 years). Further, selective survival effects may be operating among the oldest participants (Perls, Morris, Ooi, & Lipsitz, 1993; Stewart, Zelinski, & Wallace, 2000).

The results of this study imply that it is possible to study age-cognition relationships in cross-sectional studies even in the absence of information about future events such as dementia and death. However, the effect of preclinical dementia and impending death may be greater in a different type of sample. For example, in a volunteer sample, the participants may be expected to be in superior health compared to the participants in a population-based sample, resulting in smaller variability in cognitive performance and potentially greater effects of impending death and dementia.

Concluding summary: Removal of persons with preclinical dementia or in close proximity to death has a limited effect on the cross-sectional association between age and cognitive performance in a sample of very old persons of average health. This suggests that the biological aging process exerts negative influences on cognitive functioning beyond those resulting from dementia and mortality.

5.4   EARLY DETECTION OF DEMENTIA

One of the major clinical applications for findings regarding the preclinical phase of dementia concerns the possibility to identify dementia cases early on in the disease process. In this thesis, we were able to show that cognitive deficits can be an early sign of AD and VaD alike. Three years before diagnosis, we observed cognitive deficits in preclinical VaD for both episodic memory (Study I) and global cognitive ability (Study II). Thus, the demonstration of a preclinical phase with cognitive deficits in AD could be extended to VaD. The association between cognitive functioning and future dementia status remained after controlling for a history of vascular disease, taken from a computerized hospital register. This shows that, at a primary care level, where neuroimaging resources are not always available, cognitive deficits may be used as an additional source of information for identifying persons at high risk for developing VaD.

It has been suggested that measures of executive functioning should be added to the diagnostic procedure of dementia in order to improve early detection of VaD (Roman & Royall, 1999). This might allow for the identification of VaD cases without extensive memory deficits, who still have problems in their daily life. However, executive functioning is a complex cognitive domain to assess, especially in the very old who may have difficulties coping with stressful and highly demanding tasks (Bryan & Luszcz, 2000).

Although the general pattern of results indicated a somewhat greater impairment in preclinical AD than in preclinical VaD, none of the included tasks yielded performance differences between these groups. However, from a clinical perspective it may be more important to keep in mind that vascular factors may increase the risk of AD as well as

VaD (Breteler, 2000; Honig et al., 2003; Luchsinger et al., 2005). In addition, coexisting vascular lesions may worsen the cognitive deficits in clinical AD (Burns et al., 2005; Esiri et al., 1999; Petrovitch et al., 2005; Riekse et al., 2004; Snowdon et al., 1997). Primary prevention of CVD involves making lifestyle adjustments (e.g., changing dietary habits), and identifying and managing vascular risk factors (e.g., diabetes and hypertension). In persons who already have CVD, secondary prevention in the form of appropriate treatment and intensified management of risk factors might prevent or postpone the onset of severe cognitive deficits (Erkinjuntti, 1999). Interventions of this kind might prevent or delay the onset of both VaD and AD (Roman, 2003). In this context, the term VCI (Hachinski, 1994; Hachinski & Bowler, 1993) might be of value as it does not differentiate between different causes of cognitive impairment, nor does it require a clinical diagnosis. Instead, VCI directs the attention to the vascular contribution to cognitive deficits of any kind.

In Study III and IV, the focus was on the distinction between impending death and preclinical dementia. We observed, as others have done, that cognitive deficits might be related to both future death and dementia (Bennett et al., 2002; Palmer et al., 2002). However, we were also able to demonstrate that rate of cognitive decline was differentially affected in preclinical dementia. The divide between the two groups was most apparent for the MMSE, free recall of random words, and Block Design, where the impending death group declined at the same rate as the controls, whereas the preclinical dementia group showed marked cognitive decline. For word recognition, the preclinical dementia group declined twice as fast as the impending death group, although both groups showed accelerated decline compared to the controls. The impending death group only declined faster than the controls on tasks where the controls showed no significant age-related decline. Although the preclinical dementia group showed comparatively larger cognitive deficits three years before event, significant deficits were also observed for the impending death group for all cognitive tasks. Thus, given that the level of cognitive performance in preclinical dementia at a given time point is influenced both by the individual's premorbid level and time to diagnosis, an accelerated rate of decline should be a more reliable indicator of impending dementia than a low cognitive score at cross-section. As noted earlier, few other factors besides dementia have been associated with progressive cognitive decline. Thus, repeated cognitive assessments would increase the reliability when trying to identify persons who will progress to dementia within the next few years.

It should be emphasized that interindividual variability in cognitive performance and rate of cognitive change is high (Bäckman, Small et al., 2000; Bäckman, Jones, Small, Agüero-Torres, & Fratiglioni, 2003; Wilson et al., 2002), rendering differentiation between future outcomes a complex undertaking. In a meta-analysis on cognitive functioning in preclinical AD, a substantial overlap in cognitive performance was observed between preclinical AD persons and controls (Bäckman et al., 2005). Possible ways to increase the ability to identify persons at risk for developing dementia would be to combine the results from tasks measuring different cognitive domains, or to include indicators of other domains of functioning gathered from different sources, such as family interviews, clinical examination, and genetic information (Bäckman, Jones, Berger, Laukka, & Small, 2004).

34

5.5 LIMITATIONS

5.5.1 VaD diagnosis

A major limitation of the studies concerning VaD is that we lacked neuroimaging or neuropathological confirmation of the diagnosis. This made it impossible to determine the amount of degenerative pathology present in the incident VaD cases, as well as the amount of vascular pathology present in the incident AD cases. Fairly strict diagnostic criteria, corresponding to the NINDS-AIREN (Roman et al., 1993) criteria for possible VaD, were used. However, overlapping pathology might have obscured potential differences between the preclinical dementia groups. Given that brain changes in pathologically confirmed VaD and AD frequently overlap (Barker et al., 2002), mixed pathologies might be expected also in the preclinical phase.

Further, being based solely on clinical data, the VaD diagnosis was restricted to post-stroke VaD cases. Thus, we were not able to investigate patterns of cognitive deficits in other forms of VaD, such as small-vessel disease.

5.5.2 Cognitive testing

Although we investigated a broad range of cognitive domains, an area of cognitive functioning that was largely missing was executive functioning. Especially in Study I, when we contrasted the cognitive performance of incident VaD and incident AD persons, it would have been valuable to include some measures of executive functions.

Another limitation concerning the cognitive test battery is that not everyone participated in the cognitive testing, leaving us with restricted sample sizes in the studies examining specific cognitive functions. The cognitive sample might also be less representative of the general population, as more persons declined participation in the cognitive testing compared to the other parts of the assessment.

For the studies examining rate of change, the limited number of assessment points (a maximum of 3), and the relatively long follow-up intervals (3 years) did not enable us to examine the shape of cognitive decline in close detail. Rate of cognitive change prior to death and dementia is not likely to remain constant, but might be expected to accelerate at some point prior to the event.

5.5.3 Information about diseases

The KP was mainly designed to identify and follow persons with dementia. Thus, the clinical examination provides limited information regarding other diseases. We obtained information about a history of vascular disorders from the computerized Stockholm inpatient register, containing admission and discharge diagnosis from all occasions where the participants had received hospital care. Although these diagnoses can be assumed to be accurate, they likely underestimate the prevalence of vascular disorders in the sample. Whereas a stroke causes hospital admission in >90% of cases in Sweden (Alfredsson, von Arbin, & de Faire, 1986), isolated hypertension or diabetes

seldom require hospital care. In addition, we did not have information about the onset of these conditions.

5.5.4   Nature of the sample

Although the research questions examined were different for all studies included in this thesis, they were all related to cognitive functioning in preclinical dementia. As all data originated from the KP, there was some overlap with regard to participants. Therefore, the results from the five studies cannot be regarded as completely independent. This is a common problem, as it is practically impossible to perform a new longitudinal study for every research question.

The data from this thesis were taken from a population-based study with high participation rate. Thus, it should be possible to generalize the findings to other populations living in urban areas in Western societies. However, as the participants in the KP were all 75 years or older, the results may not be generalizable to populations younger than 75 years.

5.6   FUTURE DIRECTIONS

Among other things, the present thesis concerned cognitive functioning in preclinical VaD. However, as the VaD diagnosis was based solely on clinical data, we were mainly restricted to examining preclinical cognitive functioning in post-stroke VaD. One interesting avenue for future research would be to investigate preclinical cognitive functioning in other subtypes, such as small-vessel disease. Of particular interest would be to compare small-vessel VaD to post-stroke VaD and AD with regard to their relative effect on different cognitive domains (e.g., executive functioning, episodic memory), and time of onset of precipitous cognitive decline.

More research is needed on the specific effects of various vascular pathologies on cognitive functioning, both in normal aging and dementia. For example, it is important to gain further knowledge about the effects of vascular pathology on the clinical expression of AD, especially given that the vascular contribution to cognitive deficits in AD represents a factor that is amenable to prevention. In addition, few other conditions have been shown to aggravate the cognitive deficits in AD.

After controlling for preclinical dementia, we still observed significant terminal-decline effects for select cognitive tasks. This raises questions regarding what other factors might cause the effect of impending death on cognition. Is it a consequence of cumulative aging effects or can the presence of some other disease contribute to the decline in cognitive functioning? To answer these questions, more longitudinal studies with repeated cognitive assessments are needed. Ideally, these would cover the entire life span, from childhood to death.

Future research on cognitive change in old age could also employ a series of random coefficient change-point models to estimate rate of change for normative aging vs. preclinical dementia periods. Specifically, the focus concerns identifying the transition (or hinge) point where cognitive decline reliably accelerates from a normative aging

trajectory to one characteristic of preclinical dementia. To identify the average transition point that best characterizes the acceleration of decline within and across individuals, a series of time intervals in 1-month increments (e.g., 3 years, 3.1 years, 3.2 years, etc.) can be examined prior to dementia onset. Of particular interest, this novel analytic approach permits assessment of whether decline for select cognitive domains expected to be most affected by underlying pathology (e.g., episodic memory) occurs earlier than others vis-à-vis the point of incident dementia. In addition to pinpointing the onset of accelerated decline, it is also possible to specifically compare differences in magnitude of change across cognitive outcomes within the preclinical period. The same approach could be adopted to further examine the terminal decline period.

As more knowledge is obtained regarding the preclinical phase of dementia, more research is needed regarding the clinical applications of these findings. How do we identify persons on their way to developing dementia with great accuracy? Most likely, a single cognitive assessment is not enough. Despite highly significant differences at the group level, the distribution of cognitive scores between incident dementia cases and controls have been found to be largely overlapping (Bäckman et al., 2005). However, group classification may be improved by including predictors from other domains that have been linked to dementia, such as social network, activity levels, depressive symptoms, vascular risk factors, and genetic information. Combining cognitive, social, clinical, biological, and genetic markers might substantially increase prediction accuracy compared to using a single cognitive test score. Further, it would be of great interest to examine whether there are interactions between different classes of markers with regard to the probability of a future dementia diagnosis.

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8 APPENDIX

List of dissertations from Stockholm Gerontology Research Center and Aging Research Center 1991-2006

1991
Herlitz Agneta. Remembering in Alzheimer´s disease. Utilization of cognitive support. (Umeå University and Karolinska Institutet).

1992
Borell Lena. The activity life of persons with a dementia disease.

1993
Fratiglioni Laura. Epidemiology of Alzheimer´s disease. Issues of etiology and validity.
Almkvist Ove. Alzheimer´s disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.
Basun Hans. Biological markers in Alzheimer´s disease. Diagnostic implications.

1994
Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University).
Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.
Josephsson Staffan. Everyday activities as meeting-places in dementia.
Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.
Forsell Yvonne. Depression and dementia in the elderly.

1995
Mattiasson Anne-Cathrine. Autonomy in nursing home settings.
Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996
Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.
Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis).
Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997
Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.
Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis).

1998
Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

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

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

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

1999

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

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

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

2000

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

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

2001

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

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

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

2002

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

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

2003

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

2004

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

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

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study

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

Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

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

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

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

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

Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.