# Old Age Depression:

## Occurrence and Influence on Cognitive Functioning in Aging and Alzheimer's Disease

Anna-Karin Berger

Aging Research Center,
Division of Geriatric Epidemiology,
Department of Neurotec, Karolinska Institutet
and
Stockholm Gerontology Research Center

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# ABSTRACT

The general aims of this thesis were to examine the occurrence of depressive symptoms three years before the diagnoses of depression and Alzheimer's disease (AD), and to study the effects of depression on cognitive functioning in aging and AD. Five empirical studies were conducted. All data were taken from the Kungsholmen Project, a longitudinal population-based study of aging and dementia targeting persons who are 75 years and older, living in the Kungsholmen district in Stockholm, Sweden.

The specific objectives of **Study I** were to examine preclinical markers of depression, in terms of presence and severity of depressive symptoms, as well as to examine whether cognitive deficits were present during the preclinical period of old age depression. The chief aim of **Study II** was to investigate depressive symptomatology, with respect to mood- or motivation-related symptoms, in the preclinical phase of AD. In particular, Study II examined mood- and motivation-related symptoms in relation to subjective memory problems to elucidate whether depressive symptoms reflect insight into the dementing process, or is rather a part of the neurodegenerative process. **Study III** and **IV** investigated the influence of depression on AD-related deficits in various cognitive domains (e.g., episodic memory, short-term memory, verbal abilities, visuospatial skill) in mild to moderate stages of AD, whereas **Study V** examined the influence of depression on global cognitive functioning longitudinally, from the preclinical stage of AD to the time of diagnosis. Study V also addressed whether a concurrent diagnosis of depression causes more rapid decline in global cognitive functioning over a 3-year interval among persons who were going to develop AD.

Findings from **Study I** showed that depressive symptoms are elevated preclinically in old age depression. Persons who were to be depressed showed a greater number of depressive symptoms (i.e., dysphoria, appetite disturbance) and their symptoms were also more severe (i.e., dysphoria, appetite disturbance, lack of interest, psychomotor disturbances), compared to individuals who remained non-depressed. In addition, depressive symptoms were associated with somewhat poorer global cognitive functioning. These data suggest that there are preclinical markers for old age depression. **Study II** revealed that depressive symptoms are elevated in preclinical AD as well. There was a predominance of motivation-related (e.g., lack of interest, concentration difficulties, loss of energy) over mood-related (e.g., dysphoria, feelings of guilt, thoughts of death) symptoms. This pattern remained after controlling for subjective memory complaints, indicating that the elevation of depressive symptoms may not merely reflect self-perceived cognitive deficits. Thus, depressive symptoms may be a part of the pathological process of AD. The studies (**III** and **IV**) examining the effects of depression on AD-related cognitive deficits showed no impact of depression among mild to moderate cases of AD in episodic memory, verbal ability, and visuospatial skill. However, depression-related deficits in global cognitive functioning were observed in the preclinical phase of AD (**Study V**), although a diagnosis of depression did not result in greater decline over a 3-year follow-up interval.

To summarize the findings of this thesis, depressive symptoms were found to be elevated preclinically in both depression and AD. However, different patterns of symptoms were present. Mood-related symptoms were more elevated in depression, whereas motivation-related symptoms were dominating in AD. In terms of depression-related effects on cognitive functioning in AD, the results indicated that, already at a very early clinical stage of AD, the neurodegenerative process overshadows the impact of depression, although this condition is associated with cognitive deficits in normal aging.

# SAMMANFATTNING

Det övergripande syftet i detta avhandlingsarbete var att undersöka förekomsten av depressiva symtom i den prekliniska fasen, tre år före diagnos, av depression och Alzheimers sjukdom (AS). Därutöver studerades effekten av depression på kognitiva funktioner i åldrandet och vid AS. I avhandlingen ingår fem studier, vilka samtliga är baserade på data från Kungsholms-projektet, en longitudinell befolkningsstudie kring åldrande och demens hos personer 75 år eller äldre.

Det specifika syftet i **Studie I** var att undersöka prekliniska markörer för depression med avseende på förekomst och svårighetsgrad av depressiva symtom, samt att undersöka om kognitiv svikt förekommer i den prekliniska perioden vid depression hos äldre. Avsikten med **Studie II** var att studera depressiva symtom som speglar stämningsläge eller motivation i den prekliniska fasen av AS tre år före diagnos. Av speciellt intresse var att undersöka specifika symtomgruppers samband med självupplevda minnesproblem, d.v.s. huruvida depressiva symtom uppstår som en följd av insikten om den begynnande demenssjukdomen eller om depressiva symtom är en del av sjukdomsbilden i preklinisk AS. I **Studie III** och **IV** studerades effekterna av en depression i relation till nedsättningar i episodiskt minne, korttidsminne, verbala förmågor och visuospatiala färdigheter som förekommer i mild till måttlig svår AS. Slutligen i **Studie V** undersöktes effekten av depression på globala kognitiva förmågor i AS, i ett longitudinellt perspektiv, från ett prekliniskt skede tre år före diagnos och fram till diagnostillfället. Vidare undersöktes om en depression kunde medföra en snabbare försämring i globala kognitiva funktioner hos personer som kommer att utveckla AS med en samtidig depression inom en treårsperiod, jämfört med personer som enbart kommer att utveckla AS.

Resultaten i **Studie I** visade att de personer som skulle komma att utveckla en depression hade fler och svårare symtom som nedstämdhet, aptitstörningar, minskat intresse och psykomotoriska förändringar, tre år före diagnos, än personer som inte skulle komma att utveckla depression. Vidare visade resultaten att personer som skulle komma att utveckla en depression hade en sämre kognitiv funktion jämfört med personer som inte blev deprimerade tre år senare. Dessa fynd tyder på att det förekommer tidiga prekliniska tecken vid en begynnande depression hos äldre personer. Resultaten från **Studie II** visade att depressiva symtom även förekommer i den prekliniska fasen av AS. Motivationsrelaterade symtom, som minskat intresse, koncentrations-svårigheter och minskad ork, var mer framträdande än symtom som speglar stämningsläget, som t.ex. nedstämdhet. Detta resultat kunde inte förklaras av självupplevda kognitiva problem, vilket tyder på att symtomen inte enbart är orsakade av insikten om sviktande intellektuella förmågor, utan kan vara orsakade av den neurodegenerativa sjukdomsprocessen. Studierna (**III** och **IV**) kring effekterna av en depression på kognitiva förmågor hos personer med mild till måttlig svår AS, visade att depression inte ytterligare påverkade förmågor som episodiskt minne, arbetsminne, verbala förmågor eller visuospatiala funktioner. **Studie V**, däremot, visade att depressiva symtom orsakade kognitiva funktionsnedsättningar i preklinisk AS, men också att depression inte medförde någon snabbare försämring i kognitiva funktioner fram till diagnostillfället.

Sammanfattningsvis noterades förhöjda depressiva symtom i den prekliniska fasen i både depression och AS. Symtombilden varierade dock beroende på sjukdom. Symtom relaterade till stämningsläget dominerade vid en begynnande depression, medan motivationsrelaterade symtom var vanligare i preklinisk AS. Resultaten visade även att en depression inte gav någon ytterligare försämring i de kognitiva nedsättningar som förekommer i AS. Redan i ett tidigt skede av demenssjukdomen överskuggar den neurodegenerativa processen effekterna av en depression som i det normala åldrandet är starkt relaterad till kognitiva nedsättningar.

# LIST OF PUBLICATIONS

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

**Study I.**    Berger, A. -K., Small, B. J., Forsell, Y., Winblad, B., & Bäckman, L. (1998). Preclinical symptoms of major depression in very old age. A prospective longitudinal study. *American Journal of Psychiatry, 155,* 1039-1043.

**Study II.**    Berger, A. -K., Fratiglioni, L., Forsell, Y., Winblad, B., & Bäckman, L. (1999). The occurrence of depressive symptoms in the preclinical phase of Alzheimer's disease: A population-based study. *Neurology, 53,* 1998-2002.

**Study III.**    Fahlander, K., Berger, A. -K., Wahlin, Å., & Bäckman, L. (1999). Depression does not aggravate the episodic memory deficits associated with Alzheimer's disease. *Neuropsychology, 13,* 532-538.

**Study IV.**    Berger, A. -K., Fahlander, K., Wahlin, Å., & Bäckman, L. (2002). Negligible effects of depression on verbal and spatial functioning in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 13,* 1-7.

**Study V.**    Berger, A. -K., Fratiglioni, L., Winblad, B, & Bäckman, L. (in press). Alzheimer's disease and depression: Preclinical comorbidity effects on cognitive functioning. *Cortex.*

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# ABBREVIATIONS

Aß              Beta Amyloid

AD              Alzheimer's Disease

AD/D            Alzheimer's Disease and Depression

ADL             Activities of Daily Living

APOE            Apolipoprotein E

CPRS            Clinical Psychopathological Rating Scale

DSM-III-R       Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised

DMS-IV          Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

ICD-9           International Classification of Diseases, 9th Edition

LTM             Long-Term Memory

MD              Major Depression

MMSE            Mini-Mental State Examination

NINDS-ADRDA     National Institute of Neurological and Communicative Disorders–Alzheimer's Disease and Related Disorders Association

STM             Short-Term Memory

WAIS-R          Wechsler Adult Intelligence Scale, Revised

# CONTENTS

ORIGINAL PAPERS (I-V)

# INTRODUCTION

In most, if not all, countries, the number of elderly adults is increasing rapidly. According to Statistics Sweden (2003), the number of people aged 75 years and older will increase by 51 % between 2002 and 2030. As the number of very old people increases, their specific health care problems demand greater attention. This will also require an expansion of health professionals' knowledge in geriatrics and geropsychiatry.

Depression is one of the most frequently occurring psychiatric syndromes among elderly persons. Yet, it is often an over-looked and underdiagnosed disorder (NIH Consensus Conference, 1992; Unütser et al., 2002). On reason thereof may be that old age depression is difficult to recognize because of the occurrence of somatic symptoms and depression-related physical disorders (Crum, Cooper-Patrick, & Ford, 1994; Paykel & Priest, 1992; Gottfries, 2001). Many studies that have examined depression in old age have been based on clinical samples, and may thus miss a high proportion of cases, because of underdiagnosis (NIH Consensus Conference, 1992; Unütser et al., 2002).

Further, many studies have been based on retrospective data, or cross-sectional comparisons, which may not be sufficient to characterize the onset and course of depression. In order to enhance our understanding of the natural course of depression in old age, longitudinal studies are required. Identifying early signs, the type of depressive symptoms that arise first, examining the changes in symptom constellation in the development of depression should also increase the possibility of preventing this disease in old age. In the long run, unrecognized and untreated depression could lead to over-utilization of medical care and greater disability, as well as contribute to mortality (Schultz, Drayer, & Rollman, 2002) and suicide (Simon, VonKorff, & Barlow, 1995, Unützer et al., 2002). Thus, for both human (Bremner et al., 2000; McEwen & Margarinos, 2001) and economic (Bushnell & Bowie, 1995; Simon et al., 2001, Simon, VonKorff et al., 1995) reasons, it is important to improve recognition of depression in persons who may seek help for health-related problems that involve underlying depressive symptoms.

Dementia is another common, devastating, and costly disorder in elderly adults (Skoog & Olafsdottir, 2004; Wimo, 1999). In Sweden, between 150 000 and 200 000 people suffer from dementia at present. The occurrence of dementia is strongly associated with increasing age (Skoog & Olafsdottir, 2004; von Strauss, Viitanen, De Ronchi, Winblad, & Fratiglioni, 1999). Increased knowledge about the development of dementia focusing on early signs and symptoms, cognitive as well as behavioral symptoms, may have clinical implications. Specifically, by identifying individuals at risk for developing dementia as early as possible, interventions that may slow down disease progression could be implemented.

Sometimes it is hard to distinguish depression from early dementia because of overlapping symptoms (e.g., depressive symptoms as well as cognitive deficits). Increased knowledge about symptom patterns in depression and dementia may thus be helpful in differentiating these two disorders. Moreover, it is not uncommon for people to suffer from both depression and dementia simultaneously. However, the existing literature on the effects of depression on cognitive functioning in dementia is limited and inconsistent (Bäckman, Hassing, Forsell, & Viitanen, 1996; Lezak, 1995; Rovner, Broadhead, Spencer, Carson, & Folstein, 1989). In addition, most previous

research on this topic has focused primarily on episodic memory leaving other cognitive domains relatively unexplored. Thus, important research questions would be to examine the effects of depression over various cognitive domains in dementia, as well as to study the influence of depression on cognition during the progression of the dementing disorder.

The general aim of this thesis is, therefore, to examine the occurrence of depression and depressive symptoms in non-demented aging and Alzheimer's disease (AD). In addition, the thesis investigates the influence of depression and depressive symptoms on cognitive functioning in old age as well as in the progression of AD, from a preclinical phase to mild and moderate stages of the disease.

# DEPRESSION

## Definition of Depression

As noted, depression is one of the most frequently occurring psychiatric syndromes. The concept of depression includes a continuum of symptoms ranging from dysphoria, which may affect almost everyone from time to time, to a diagnosed depressive disorder (Paykel & Priest, 1992). However, it is of importance to separate between depressive symptoms and a clinical diagnosis of depression. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994), major depression (MD) is characterized by depressed mood or loss of interest and pleasure for things most of the day over a two-week period or more. The symptoms stated in the criteria for MD are: dysphoria/depressed mood, lack of interest, weight change/appetite disturbance, sleep disturbance, psychomotor disturbance, loss of energy, feelings of guilt/worthlessness, thinking/concentration difficulties, and suicidal thoughts/ideation. In order to receive a diagnosis, the person must present with five or more out of the nine symptoms, one of which has to be either depressed mood or loss of interest. In addition, MD must be separated from mania, effects of substance abuse or pharmacological treatment, general medical condition, and bereavement.

Dysthymia is a milder form of depression. Both major depression and dysthymia involve essentially the same depressive symptoms, but they differ in severity and duration. The symptoms for dysthymia are: weight change/appetite disturbance, sleep disturbance, loss of energy, thinking/concentration difficulties, low self-esteem, and feelings of hopelessness (DSM-IV; American Psychiatric Association, 1994). Dysthymic disorder is a somewhat less pronounced depressive disorder compared to MD, but has a longer duration and is more chronic in nature. The criteria for a clinical diagnosis of dysthymic disorder require decreased mood during most days for at least two years.

It may be noted that there are several other depressive disorders represented in the DSM-IV manual, but this thesis only focuses on MD and dysthymic disorder.

## Depression in Old Age

The prevalence of depressive disorders among people 65 years and older ranges between 10-15% (Gottfries, 2001; Pálsson et al., 2001). Prevalence rates for those who suffer from severe depression such as MD vary between 1-10% (Blazer, Huges, & George, 1987; Forsell, Jorm, Fratiglioni, Grut, Winblad, & 1993; Pálsson et al., 2001; Snowdon & Lane, 2001). A recurrent discussion has concerned whether depression is more common in old age than in younger ages (Hocking, Koenig, & Blazer, 1995; Horwath & Weissman, 1995). Yet, there is no clear answer to that question, but as the severity of health problems increases, the rate of depression likewise rises (Hocking et al, 1995).

The cause of depression in old age is clearly multi-factorial and several risk factors have been identified, including disabilities in daily living (Bosworth, Hayes, George, & Steffens, 2002; Bruce, 2002; Kivelä, Kongäs-Saviaro, Pahkala, Kesti, & Laippala, 1996), lack of social support (Bosworth

et al., 2002; Bruce, 2002), institutionalization (Fröjdh, Håkansson, Karlsson, & Molarious, 2003; Kivelä, et al., 1996), declining health (Bruce, 2002; Kivelä, et al., 1996; NIH Consensus Conference, 1992), and drug therapy (Gottfries, 2001). Increasing age also results in an increase in lifetime risk of exposure to stressful life events and personal losses (Bruce, 2002; Horwath, Johnson, Klerman, & Weissman, 1992; Fiske, Gatz, & Pedersen, 2003; Kraaij, Arensman, & Spinhoven, 2002). In addition, there is an increase in the occurrence of depression in age-related neurodegenerative diseases such as AD, vascular dementia, and Parkinson's disease (Caine, Lyness, & King, 1993, Gottfries, 2001). Predisposing familial and genetic factors are also contributing risk factors in depression, but are not as potent as in younger depressed individuals (Baldwin & Thomenson, 1995; Paykel & Priest, 1992).

The diagnostic criteria for depression, as defined in DSM-IV, are the same for elderly adults as for younger people. However, diagnosing depression in old age is sometimes problematic. There are several reasons for these difficulties, which may be related to the fact that depression is an underdiagnosed disorder in the elderly. For example, young and older adults often report different symptoms. Rather than reporting depressed mood, elderly people tend to report more diffuse symptoms or somatic complaints (e.g., aches and pains, stomach problems, memory difficulties, worrying, anxiety, irritability, aggression) that fit poorly the diagnostic criteria of depression (Hocking et al., 1995; NIH Consensus Conference, 1992). Further, some of the criteria for depression may be less relevant in old age and may be hard to judge (Forsell, Jorm, von Strauss, & Winblad, 1995). For example, in DSM-IV, the criterion C includes a statement that the mood status must cause impairment in occupational and social functioning, which may not be applicable in old age, as most elderly people are retired and many have limited social networks. In addition, criterion D indicates that the depression should not be caused by a general medical condition or caused by side effects of pharmacological treatment. This is clearly a problem considering the increase of health problems with advancing age. The development of depression in old age can be both abrupt or have a more gradual onset (Berg et al., 2001). As to the latter possibility, there is growing evidence that the development of depression in very old adults is a process that can take many years (Fröjdh et al., 2003; Sharma, Copeland, Dewey, Lowe, & Davidson, 1998). A gradual onset may contribute to the difficulties in recognizing depression in elderly persons and further increase the risk for depression to become more chronic in nature than earlier in life. Taken together, these considerations make it likely that depression is an underdiagnosed disorder in old age.

## DEMENTIA

### Definition of Dementia

One of the most commonly used clinical definitions of dementia is stated in DSM-IV (American Psychiatric Association, 1994). Dementia is a clinical syndrome characterized by deterioration in multiple cognitive domains including memory impairment accompanied by at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or deficits in executive functioning. Moreover, the symptoms must be severe enough to interfere with social or occupational life, and have to represent a decline from previous levels of functioning. Further, a dementia diagnosis is not rendered if the symptoms occur exclusively during the course of delirium.

Prevalence rates for dementia vary considerably across studies, depending on the diagnostic criteria employed (e.g., DSM vs. ICD), the sampling techniques used, and the sensitivity of the instruments used to identify cases (Kaszniak & Christenson, 1997). However, a consistent observation is that the prevalence of dementia is strongly age-related. Evidence suggests that the number of people with dementia double for every five-year interval from 60 years and onwards (Jorm, Korten, & Hendersson, 1987). Representative data on the prevalence of dementia in late life are shown in Figure 1.
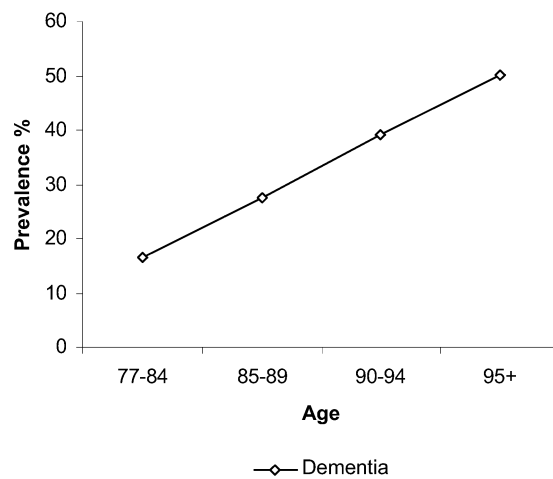


**Figure 1**. Prevalence of Dementia Across Age (modified from von Strauss et al., 1999)

## Alzheimer's Disease

Alzheimer's disease (AD) is the main subtype of dementia accounting for between 50-70% of all dementia cases (Cummings & Benson, 1992; Fratiglioni, De Ronchi, & Agüro-Torres, 1999; Fratiglioni et al., 2000). AD is characterized by slowly progressive loss of cognitive functioning. According to DSM-III-R criteria for AD, this disease has a gradual onset and continuing cognitive decline with no change of consciousness. A clinical diagnosis of AD is made by excluding other conditions (e.g., MD, schizophrenia), on the basis of a thorough physical examination and laboratory tests. Another commonly used diagnostic scheme is the one derived from the workgroup on diagnosis of AD established by the National Institute of Neurological and Communicative Disorder and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA: McKhann et al., 1984), which is similar to the DSM criteria, with the addition of a continuum that ranks the certainty of the AD diagnosis from possible to probable to definite AD (the latter form is obtained from histopathological data).

The diagnosis of AD is complicated by the fact that this disease has a rather long preclinical period during which deficits are observed in a variety of cognitive domains such as episodic memory (Bäckman, Small, & Fratiglioni, 2001; Chen et al., 2001), executive functioning (Albert, Moss, Tanzi, & Jones, 2001; Chen et al., 2001), perceptual speed (Fabrigoule et al., 1998), verbal ability (Jacobs et al., 1995), and visuospatial skill (Small, Herlitz, Fratiglioni, Almkvist, & Bäckman, 1997).



**Figure 2**. Cognitive Decline in Aging and Dementia
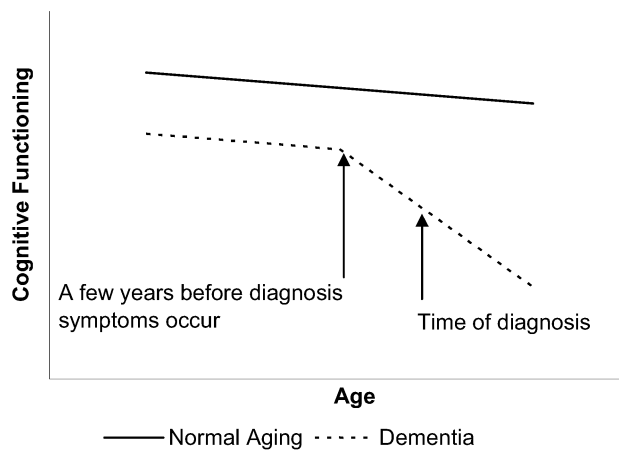
As illustrated in Figure 2, the preclinical neurodegenerative processes in AD are probably going on for decades at a nonsymptomatic stage before precipitous decline occurs that eventually results in a clinical diagnosis (Nordberg, 2003). The histopathological hallmarks of AD are neurofibrillary tangles and the aggregation of beta-amyloid (Aβ) in senile plaques. According to the

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amyloid-cascade hypothesis (Hardy & Selkoe, 2002), the accumulation of Aβ is followed by a sequence of pathogenic events leading to neuronal loss. Early on in the disease process, there are structural and functional alterations in the brain. These include, but are not limited to, volume reductions in the medial temporal lobe (Fox et al., 1996) and frontal cortex (van der Flier et al., 2002), white-matter hyperintensities (Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000), decrease in blood flow (Kogure et al., 2000), and reductions in whole brain glucose metabolism (Silverman et al., 2001).

The etiology of AD is yet unknown. There are a variety of potential risk factors that have been examined, such as genetic factors (e.g., apolipoprotein E [APOE] ε4 genotype; familial aggregation βAPP, presinilin 1 and 2; Down's syndrome), biological factors (e.g., high age, female gender, high and low blood pressure, cardiovascular diseases, diabetes, cerebrovascular factors, depression, hypothyroidism, vitamin $B_{12}$, and folic acid deficiency), environmental factors (e.g., occupational exposure, diet, smoking, alcohol, head trauma, aluminum exposure), and social factors (e.g., low education, personality, poor social network, limited leisure activities). There are few risk factors that are commonly agreed upon. However, old age, familial aggregation, APOE ε4 genotype, and Down's syndrome are factors known to increase the risk of AD. In addition, there are several possible risk factors for AD that have been discussed in the literature such as female gender, vascular factors, alcohol consumption, and poor social network (for an overview, see Fratiglioni & Rocca, 2001). Given the heterogeneity of symptoms in AD and the variety of possible risk factors, there are probably different underlying etiologies among different persons.

## Depression in Alzheimer's Disease

Depression and dementia are both prevalent disorders in old age and may co-occur in the same individual. Reported prevalence rates of depression in AD are considerably higher than among non-demented elderly persons, varying from 4 to 51% (Forsell et al., 1993; Greenwald, et al., 1989; Migliorelli et al., 1995; Snowdon & Lane, 2001; Rovner et al., 1989; Vida, Des Rosiers, Carrier, & Gauthier, 1994). The large variation across studies may reflect differential sensitivity in the instruments used when screening for depression as well as the stage of dementia at assessment (e.g., mild, moderate, severe, for an overview see Kaszniak & Christenson, 1997).

Some researchers have argued that the occurrence of depression in dementia may be a subjective reaction to the ominous outlook for the future (Lyketsos et al., 1997; Migliorelli et al., 1995), whereas others have contended that depression is rather a reflection of changes in the brain (Nordberg, 1992; Sultzer, 1996). Obviously, these two possibilities are not mutually exclusive. However, there is emerging evidence to support the idea that depression or depressive symptoms in early dementia is not primarily caused by emotional reactions due to insight into the dementing process (Ballard, Cassidy, Bannister, & Mohan, 1993; Cummings, Ross, Absher, Gornbein, & Hadjiaghai, 1995; Verhey, Rozendaal, Ponds, & Jolles, 1993).

It is commonly observed that the frequency of depression in AD decreases with increased dementia severity (e.g., Cummings, Miller, Hill, & Neshkes, 1987). Several hypotheses have been proffered to account for this observation. One possibility is that cognitive dysfunction results in poorer ability to communicate symptoms (masking hypothesis), and another is that the deterioration of brain functions decreases the ability to experience complex feelings (the extinction hypothesis;

Helmchen & Linden, 1993; Zubenko, Moossy, & Kopp, 1990). Further, depression is hard to diagnose among demented persons, because the criteria require the symptoms to be present for a certain time period. Many demented people have difficulties in reporting the onset of symptoms and may lack relatives who can report this information. Conceivably, these facts contribute to the lower frequency of depression in later stages of the disease.

Previous studies have examined specific depressive symptoms during the course of dementia (Forsell et al., 1993). Based on factor-analytic work, the symptoms of depression have been divided into two categories reflecting either mood- or motivation-related symptoms of MD. It has been found that mood-related symptoms (dysphoria, appetite disturbance, feelings of guilt/worthlessness, thoughts of death) are more common in the earlier stages of the disease, whereas motivation-related symptoms (lack of interest, concentration difficulties, loss of energy, psychomotor disturbances) increase across the pathogenesis. A similar trajectory of depression-related symptoms in AD was observed in a recent longitudinal study by Gilley, Wilson, Bienias, Bennet and Evans (2004). A higher frequency of mood symptoms may be regarded as more typical for depression and, therefore, it may be easier to recognize a depressive disorder in early dementia. When motivation- or somatic-related symptoms dominate, these symptoms may seem reflect cognitive or behavioral problems rather than a depressive disorder. As a result, depression may be particularly likely to be underdiagnosed in later stages of dementia.

## COGNITIVE FUNCTIONS

Cognition is a concept that can be defined by all mental activities involved in acquisition, processing, storage, and retrieval of information. This concept includes the use of a variety of functions such as memory (short-term and long-term), learning, abstraction, logical thinking, perception, attention, verbal ability, and visuospatial skill (Flavell, 1985)

In the following subsections, a description of the cognitive domains examined in this thesis will be provided. These cognitive domains will be further discussed in terms of age-related differences, and regarding the influence of depression and AD.

### Memory

Human memory has been conceptualized in terms of different interrelated subsystems, where every subsystem has its specific function (e.g., Tulving, 1983, 1993). An overview of different memory systems is portrayed in Figure 3.
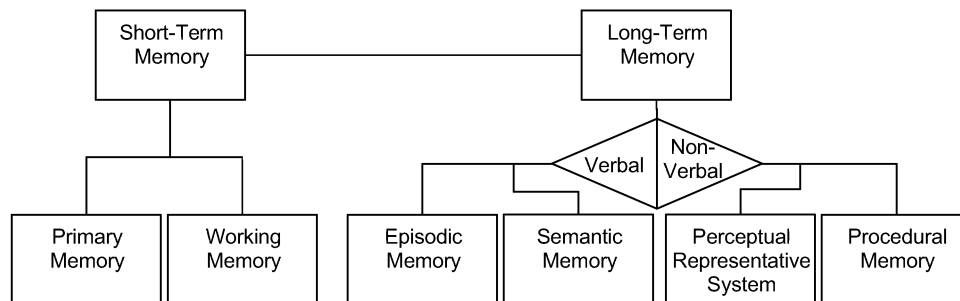
**Figure 3**. Overview of Human Memory Systems (modified after Squire, 1992 and Baddeley, 1986)

At the first level, human memory can be divided into short-term (STM) and long-term memory (LTM). LTM is characterized by more or less permanent and unlimited storage, whereas STM is characterized by temporary storage of information depending on maintenance of attention. STM is also involved in forming new memories that are to be stored in LTM.

### Short-Term Memory

STM can be further divided into primary memory and working memory. Primary memory reflects a relatively passive way of holding information in mind for a limited period of time. For example, when you search for a number in the phone book you are able to keep the number in mind until you have dialed it, and then the information usually vanishes when your attention is shifted into another direction. By contrast, working memory reflects the active processing of information while maintaining and integrating old information and experiences from LTM (e.g., goals,

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strategies), in a conscious manner (Baddeley, 1986). Research indicates that primary memory is little affected in normal aging (Gregoire, Linden, & Van der Linden, 1997; Wahlin, Bäckman & Winblad, 1995). However, working memory, requiring simultaneous storage and processing of information, shows clear age-related deficits (e.g., Hultsch, Herzog, & Dixon, 1990; Salthouse & Babcock, 1991).

**Long-Term Memory**

LTM can be decomposed into four subsystems: procedural memory, which is expressed through automatically and skilled behavioral and cognitive procedures, usually without conscious recollection (e.g., riding a bike, swimming, driving a car); perceptual representation system (PRS), which is primarily concerned with identification of perceptual objects, also operating disconnected from consciousness; semantic memory, which deals with acquisition and use of factual knowledge; and episodic memory, which involves memories of personally experienced events. The ordering of systems corresponds to their developmental sequence in both a phylogenetic and an ontogenetic sense. Procedural memory arises first from infancy to adulthood, then the capacity to acquire knowledge about the world arises, and the last to develop is episodic memory (Suddendorf & Corbalis, 1997). Due to the content of this thesis, episodic and semantic memory will be further described and distinguished with respect to their function (e.g., Tulving & Markowitsch, 1998).

**Episodic memory**. Episodic memory deals with everyday happenings encoded in a particular time and place. This form of memory involves traveling backwards in time to remember personally experienced events through conscious recollective processes (Wheeler, Stuss, & Tulving, 1997). Episodic memories can be of autobiographical character, such as when you remember what you had for breakfast this morning, or where you spent your last vacation, but they can also deal with less personal information such as remembering a noun from a word list. Episodic information is processed in three steps: encoding, storage, and retrieval. At the encoding stage memory traces are established. Encoding can be both intentional (e.g., active learning) and incidental (a byproduct of some other cognitive activity). In the storage stage, memory traces are retained in long-term memory for later use. The retrieval stage deals with recovering of memory traces, activating previously encoded information at a given occasion, through recall or recognition. Free recall, to remember things with little support, is more difficult than to make a judgment as to whether a certain piece of information is familiar or not in a recognition test. In experimental settings, episodic memory is typically assessed by having the person to remember some specific information (e.g., lists of words or pictures) acquired in the laboratory. In investigating episodic memory, experimental variations may be made both at the encoding phase (i.e., instructions, materials, procedures) and at the retrieval phase (e.g., free recall, cued recall, recognition).

Episodic memory draws on distributed neural networks, the specific sites depending on the characteristics of the information (e.g., verbal information processing involves left-hemisphere regions to a greater extent than non-verbal processing which involves more regions in the right hemisphere) and the type of process carried out (e.g., encoding: left frontal areas and hippocampal regions vs. retrieval: right frontal areas and more posterior regions, for an overview see Cabeza & Nyberg, 2000). Episodic memory has been found to be vulnerable to a number of conditions that affect brain functioning (e.g., aging, dementia, depression, schizophrenia). One reason thereof may

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be the widespread network of brain structures involved (e.g., hippocampus, diencephalon, cerebellum, thalamus, anterior cingulate gyrus, prefrontal cortex, and temporal and parietal cortex). Thus, lesions at multiple sites in the network may disrupt performance in episodic memory tasks (Cabeza & Nyberg, 1997: Kolb & Wishaw, 1996).

There is strong evidence for age-related deficits in episodic memory (for a review, see Bäckman, Small, & Wahlin, 2001). Findings from two large-scale studies including subjects from the ages of 35 through 80 years of age (Nilsson et al., 1997) and from late teens through mid 90s (Salthouse, 1998), reveal three general trends concerning the pattern of age-related deficits in episodic memory: (1) the onset of decline appears to occur earlier in life than commonly thought; (2) the deterioration is gradual rather than discrete; and (3) the rate of decline is relatively slow.

**Semantic memory**. In contrast to episodic memory, semantic memory is not personal or context-bound. Rather, it stores memories about our general knowledge of the world, facts including meaning of words, concepts, and symbols, their associations, and the rules for using these concepts and symbols. Examples of information stored in semantic memory include that Stockholm is the capital of Sweden, that $H_2O$ is the chemical formula for water, and that apple and banana both share the common feature that they are fruits.

Semantic memory is often involved when testing other cognitive functions such as verbal (e.g., word generation, word knowledge) and visuospatial (e.g., construction and perceptual knowledge) abilities. Semantic retrieval involves specific activity patterns in the temporal, occipital, and frontal lobes depending on the type of information processed (Cabeza & Nyberg, 2000).

Many aspects of semantic memory (e.g., vocabulary, semantic priming) seem to be relatively resistant to the normal aging process. As long as the person is well and healthy new facts and knowledge can be stored in semantic memory. However, some researchers have observed age-related semantic memory deficits. Specifically, elderly people show problems in accessing information from semantic memory rapidly, as illustrated by difficulties in remembering proper names (Crook & West, 1990), generating items in verbal fluency tests (Bäckman & Nilsson, 1996), naming common objects (Au et al., 1995; Mitrushina & Satz, 1995), and producing words from definitions (Maylor, 1990). Thus, the pattern of age similarities and differences in semantic memory suggests that, although the structure of the semantic network is well preserved in aging, there are age-related impairments in lexical access (e.g., Light, 1992).

## Verbal Abilities

Verbal abilities are predominantly depending on structures and networks in the left hemisphere of the brain among most right-handed individuals (Lezak, 1995). Through lesion studies with aphasic patients different brain areas have been related to basic language functions. Language production has been shown to rely heavily on Broca's area (in the left inferior frontal lobe), whereas Wernicke's area (in the left superior posterior temporal lobe and the inferior parietal lobe) is particularly critical to language comprehension. However, it should be noted other areas than these (e.g., association cortex) is involved in language processing as well (Kolb & Wishaw, 1996).

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Verbal skills can be assessed by means of tests of naming, comprehension, and production. In this thesis, verbal functioning is assessed with verbal fluency tasks that measure language production. In these tasks, subjects are instructed to generate words starting with a specific letter, or to generate words from a certain category (e.g., animals, food, professions). Although both types of fluency tasks involve semantic search, category fluency is supposed to put greater demands on the integrity of the semantic network than letter fluency (e.g., Chan, Butters, & Salmon, 1997; Hodges & Patterson, 1995; Monsch et al., 1994). As alluded to above, aging negatively affects the rapid access of information from semantic memory, which may further cause effects in other cognitive functions such as episodic memory (Bryan & Luszcz, 2000; Hultsch, Herzog, Dixon, & Small, 1998).

## Visuospatial Abilities

Visuospatial skills draw primarily on the right hemisphere of the brain. However, visual information is processed in both the left and right hemispheres involving structures in the occipital, temporal and parietal lobes (Kolb & Wishaw, 1996). Visual information is first processed into visual cortex in the occipital lobes. From the visual cortex, information is then processed through two different pathways: (a) the dorsal stream from visual cortex to parietal areas; this system is concerned with *where* the visual information is located; and (b) the ventral stream from visual cortex to temporal areas; this system is concerned with *what* the visual information represents.

Visuospatial abilities include analyzing spatial information (visual perception) as well as constructional skills. Age-related deficits in visuospatial skills are typically observed in tasks requiring constructional skills (Ivnik et al., 1992; Storandt, 1977). Some researchers have attributed age-related visuospatial impairments to deficits in speed of information processing, both with regard to perceptual and psychomotor speed (Salthouse, 1982). This assertion is related to the fact that visuospatial tests (i.e., Block design) are often administered under time restrictions; a faster answer results in a higher score. However, Storandt (1977) demonstrated significant age differences between young and older adults even when faster solutions were not credited and when no time limits were imposed. This suggests that factors in addition to processing speed may contribute to age-related deficits in visuospatial functioning.

## Correlates of Cognitive Functioning in Old Age

Numerous factors have been examined as sources of variability in cognitive functioning in old age (for a review, see Bäckman, Small & Wahlin, 2001). These include demographic factors (e.g., age, sex, years of education), life-style factors (e.g., activity patterns, substance use), health-related factors (cardiovascular disease, diabetes, vitamin $B_{12}$ and folic acid deficiency, depression, dementia), and genetic factors (e.g., APOE status). In the following section, the cognitive repercussions of the disease-related factors targeted in this thesis, depression and dementia, will be discussed.

## Cognitive Functioning in Depression

Most cognitive studies of depressed persons have focused primarily on episodic memory functions (Lezak, 1995). It has been consistently shown that subjective memory complaints are more common in old age depression than among younger depressed persons (Feehan, Knight & Partridge, 1991; Grut et al., 1993; Williams, Little, Scates, & Blockman, 1987). However, some investigators have failed to find corresponding differences between depressed and non-depressed elderly persons on objective memory measures (Bäckman, Hassing et al., 1996; O'Connor, Pollit, & Roth, 1990; O'Hara, Hinrichs, Kohut, Wallace & Lemke, 1986; Williams et al., 1987), whereas others have reported depression-related episodic memory deficits (Bäckman & Forsell, 1994; Burt, Zembar, & Niederehe, 1995; Hart, Kwentus, Hamer & Taylor, 1987; La Rue, 1989; La Rue, Swan & Carmelli, 1995). In two meta-analyses on depression and episodic memory (Burt et al., 1995; Kindermann & Brown, 1997), there was a significant relationship between depression and episodic memory impairment. Further, the episodic memory deficits were more pronounced in younger cohorts of adults. This finding may reflect the fact that episodic memory deteriorates in old age, thus reducing the room for further impairment due to depression in tasks typically used to assess episodic memory.

Possible factors contributing to the inconsistent findings regarding depression and memory are sample selection (e.g., clinical or population-based samples), type of depression studied (i.e., diagnostic procedure, severity), and the way in which episodic memory was assessed (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Christensen, Griffiths, Mackinnon, & Jacomb, 1997). As to the later, larger effects of depression are often seen in tasks that require effortful elaboration (e.g., free recall) than in tasks providing more cognitive support (e.g., recognition, cued recall; Bäckman & Forsell, 1994; Hartlage Alloy, Vazquez, & Dykman, 1993).

Other research has extended depression-related deficits to other cognitive functions, including executive functioning (Degl'Innocenti, Ågren, & Bäckman, 1998), psychomotor speed (Austin et al., 1992), verbal abilities (Emery & Breslau, 1989; King, Caine, Conwell, & Cox, 1991; Ravnkilde et al., 2002; Veiel 1997), visuospatial functioning (Abas, Sahakian, & Levy, 1990; Veiel, 1997), and attention (Landrö, Stiles, & Sletvold, 2001). Thus, depression seems to impair cognitive functioning in old age in a relatively generalized manner.

Some theorists have suggested that depression is associated with a reduction of basic processing capacity (Hartlage et al., 1993), whereas others have asserted that motivational problems (e.g., pessimistic thoughts, lack of interest) result in cognitive deficits, although the cognitive resources may be preserved (Miller, 1975, Bradley & Mathews, 1983). A third view attributes the deficits to a narrowing of attention to specific depressive content (i.e., mood-congruent memory bias: Blaney, 1986; Bradley, Mogg, & Williams, 1995). Further, some theories focusing specifically on episodic memory deficits argue that depression-related impairments reflect a general retrieval deficit, supported by data indicating poorer performance on free recall but not in recognition among depressives (Massman, Delis, Butters, Dupont, & Gillin, 1992, Ilsley, Moffoot, and O'Caroll, 1995). However, other research reports that depressed individuals perform worse in recognition tasks too, suggesting that encoding deficits cannot be ruled out (Kindermann & Brown, 1997).

In a meta-analysis by Christensen and colleagues (1997), the effects of depression were examined across a variety of cognitive domains in subjects 60 years and older, including both

clinical and population-based samples. These authors also investigated influences of subject characteristics such as age, severity of depression, type of depression (i.e., bipolar, unipolar, dysthymia), and diagnostic instrument (i.e., clinician ratings vs. DSM criteria). In addition, Christensen et al. examined effortful (e.g., constructional skills, story comprehension, free recall) vs. non-effortful (e.g., naming, vocabulary, word comprehension, recognition) tasks in differentiating depressives from controls. Further, mood-congruent memory bias was examined in episodic memory tasks (i.e., whether depressed persons remember unpleasant materials better than neutral or pleasant materials).

The results revealed widespread cognitive deficits in depression. Severity of depression and diagnostic instrument used were associated with larger effect sizes, whereas type of depression did not affect the magnitude of impairment. The latter finding stands in contrast with findings reported in younger samples (e.g., Airaksinen et al., 2004). When contrasting depressives and controls in tasks requiring effortful versus non-effortful processing, there were no differences as a function of type of processing: depressed persons did worse in both conditions, which is inconsistent with some previous findings (see Hartlage et al., 1993). However, Christensen et al. found that tasks assessing problem solving, episodic memory, and speed were particularly difficult for depressed individuals.

Returning to the theories described above, the results from the meta-analysis did not support the notion that effortful but not non-effortful tasks are impaired in depression. The findings provide partial support for the "motivational" view that there is loss of functioning across a variety of cognitive domains including memory, speed, attention, construction/tracking, and conceptual tasks. Nevertheless, there were some differential effects; all tasks were not affected to the same extent, indicating that "a global motivational deficit" cannot fully account for the findings. Further, the narrowing of attentional range hypothesis was also partly supported by findings of unimpaired performance on unpleasant compared to pleasant materials. The critical point, though, is that the latter hypothesis does not address the speed and conceptual impairments, or the global extent of the deficits. Thus, further research is needed to provide a more complete understanding of the origins of depression-related cognitive deficits.

In addition to psychological theories of cognitive deficits observed in old age depression, there are neurobiological findings suggesting that depressive disorders are associated with structural and functional brain changes. Imaging studies demonstrate volume reductions in frontal and medial temporal lobe areas, such as the hippocampus (Bremner et al., 2000; Kim, Payne, Levy, MacFall, & Steffens, 2002; McEwen & Magarinos, 2001; Sheline, Wang, Gado, Csernansky, & Weiner, 1996) and the amygdala (Sheline, Gado, & Price, 1998), decreased frontal glucose metabolism (Drevets, 2000), and decreased blood flow in striatal, frontal, and temporal regions (Bench, Friston, Brown, Frackowaik, & Dolan, 1993; Drevets et al., 1997; Mayberg, Lewis, Regenold, & Wagner, 1994). These pathological findings have been found to be present early in the disease process (Manji, Drevets, & Charney, 2001), and the affected brain regions are known to be critical to multiple cognitive processes (Bhalla & Iyengar, 1999; Liotti & Mayberg, 2001).

### Progression of Cognitive Deficits in Alzheimer's Disease

It is well established that AD has a long preclinical period during which cognitive impairment is detectable (Albert et al., 2001; Bäckman, Small & Fratiglioni, 2001; Chen et al., 2001; Grober, Lopton, Hall, & Crystal, 2000; Lambon-Ralph, Patterson, Graham, Dawson, & Hodges, 2003; Small, Fratiglioni, Viitanen, Winblad, & Bäckman, 2000). However, the length of this preclinical period is unclear. Longitudinal studies have found cognitive deficits already seven up to approximately some ten years before diagnosis (Bäckman, Small, & Fratiglioni, 2001; Elias et al., 2000). Various cognitive abilities have been examined in order to identify future AD cases. Episodic memory tasks have turned out to be one of the most prominent measures in predicting forthcoming AD, as measured with recall (e.g., Albert et al., 2001; Bäckman, Small, & Fratiglioni, 2001; Elias et al., 2000; Small, Herlitz et al., 1997) or recognition (e.g., Bäckman, Small, & Fratiglioni, 2001; Small, Herlitz et al., 1997), as well as for verbal (e.g., Albert et al, 2001; Small, Herlitz et al., 1997), and non-verbal (e.g., Albert et al., 2001; Small, Herlitz et al., 1997) materials.

In addition, other cognitive domains have also revealed poorer performance years before the AD diagnosis. These include verbal ability (e.g., Albert et al., 2001; Chen et al., 2001; Small, Herlitz et al., 1997, Snowdon et al., 1996), attention (e.g., Chen et al., 2001; Linn et al., Tierney et al., 1996), and executive function (e.g., Albert et al., 2001; Chen et al., 2001; Whalley et al., 2000). The widespread affection of cognitive abilities prior to the dementia diagnosis is consistent with imaging findings showing that multiple brain structures and functions are altered in the preclinical phase. These changes include volume losses in the medial temporal lobe (Fox et al., 1996) and frontal cortex (van der Flier et al., 2002), white-matter hyperintensities (Wolf et al., 2000), and reductions of whole-brain glucose metabolism (Silverman et al., 2001). It is of interest to note that there are many similarities with regard to the brain regions affected in depression and prodromal AD, although the degree of affection is more widespread and severe in AD.

One of the hallmarks of AD is memory problems as stated in the diagnostic criteria. These problems are obvious and extensive at the time of diagnosis. All memory systems seem to be affected by the pathological processes of the disease, but the degree of deficit varies across different forms of memory. Like in normal aging, episodic memory is most sensitive to pathological changes related to the AD process (Almkvist & Bäckman, 1993). Other types of memory such as semantic memory (Chan et al., 1997; Hodges & Patterson, 1995) and working memory (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986) also seem to be affected early on in the disease process. By contrast, primary memory processes are relatively well preserved (Morris, 1992; Morris, 1996; Simon, Leach, Wincour, & Moscowitch, 1995). Despite the widespread memory impairment in early AD, these patients are able to benefit from cognitive support for improving memory. However, a common observation is that AD patients require support both at encoding (e.g., more study time) and retrieval (e.g., cues) to exhibit memory facilitation (e.g., Almkvist, Fratiglioni, Agüero-Torres, Viitanen, & Bäckman, 1999).

Although memory problems may dominate in early-stage AD, other cognitive abilities start to show more dramatic changes with increasing dementia severity. Mapping the rate and order of decline across various cognitive domains after the time of diagnosis, longitudinal studies (e.g., Almkvist & Bäckman, 1993; Grady et al., 1988; Small & Bäckman, 1998) have found the most dramatic changes in cognitive performance of mildly demented old adults to occur in measures of verbal and visuospatial abilities. This may reflect the fact that the room for further deterioration in

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episodic memory is limited, because AD patients have marked deficits in this form of memory already preclinically.

Viewing the pathological processes in dementia as continuous, where the disease affects various cognitive abilities at different stages and to a different extent along the course, it is conceivable that different individual-difference variables (e.g., age, sex, education, depression) may influence various cognitive abilities at different stages of the dementing disease. However, most research has failed to demonstrate effects of such individual-difference variables on cognitive performance and decline in AD, although the variables examined are known to influence performance among non-demented elderly adults (Bäckman, Hill, Herlitz, Fratiglioni, & Winblad, 1994; Buckwalter, Sobel, Dunn, Diaz, & Henderson, 1993; Katzman, Brown, Thal, Aronson, & Butters, 1983; for a review, see Bäckman, Small, Wahlin, & Larsson, 1999).

## Comorbidity Effects of Depression and AD on Cognitive Functioning

Research examining the effects of depression on cognitive functioning in AD patients lacks consistency (e.g., Bäckman, Hassing et al., 1996; Lopez, Boller, Becker, Miller, & Reynolds III, 1990; Pearson, Teri, Reifler, & Raskind, 1989; Rovner et al., 1989). Most research addressing this issue has focused on global cognitive ability (e.g., Mini-Mental State Examination; Folstein, Folstein, & McHugh, 1975) or episodic memory. For example, Rovner and colleagues (1989) reported that depressed AD patients were more impaired on the MMSE than were AD patients without concomitant depression. On the contrary, Pearson et al. (1989) found depressed AD patients to be less impaired than AD patients without depression, again using the MMSE as the outcome measure. Interestingly, Pearson et al. (1989) found the depressed group to be more functionally impaired as assessed by the Katz ADL index (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963), a finding that has received support in other research (e.g., Forsell & Winblad, 1998). In a longitudinal report (Lopez et al., 1990), it was suggested that depression does not modify the cognitive profile in AD or the rate of progression. Finally, examining a population-based sample of nonagenarians, Bäckman and colleagues (1996) found that major depression did not exacerbate the episodic memory deficits in AD.

However, there are several issues that need to be considered in interpreting these negative findings. First, the sample in the Bäckman et al. (1996) study consisted of very old adults (90-100 year olds). Meta-analyses have documented that potential effects of depression may be more likely to occur in younger cohorts of old adults (see Burt et al., 1995; Kindermann & Brown, 1997). Hence, the sample in the Bäckman et al. (1996) study may have been too old in order to reveal depression-related deficits in AD. Second, when examining depression-related cognitive deficits in dementia careful attention needs to be paid to the matching of individuals with or without depression on dementia severity. Oftentimes groups are matched on the basis of a global cognitive measure (e.g., the MMSE). However, both depression and dementia are associated with cognitive deficits. Hence, matching on a global cognitive instrument may yield groups that are not comparable in terms of dementia severity. This may result in findings showing no depression-related effects on cognition in dementia. Third, depression may have greater impact on cognition during different stages of the disease (e.g., preclinical, mild, moderate, severe). For example, the depressed-demented group in the Rovner et al. (1989) study was more severely demented based on

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the MMSE ($M = 9.5$, $SD = 6.7$), compared to the depressed-demented persons in the Bäckman et al. (1996) study who were more cognitively intact ($M = 18.1$, $SD = 4.0$). Thus, it is possible that Rovner et al. (1989) would not have observed an association between depression and cognitive functioning in dementia in an earlier stage of the disease.

A further factor concerns the outcome measures used. Whereas Bäckman et al. (1996) focused exclusively on episodic memory functioning, Rovner et al. (1989) sampled from a number of domains of functioning, through their use of the MMSE. Thus, had a wider variety of measures (e.g., tasks assessing verbal, visuospatial, and psychomotor speed) been used by Bäckman et al. (1996), some differences may have been observed. In addition, it should be noted that neuropsychological tests assessing specific domains of cognitive functioning are not corresponding directly to the MMSE. The MMSE with its subscale scores ranging from 1-5 may easily suffer from floor effects in these types of samples. Thus, an interesting pursuit would be to examine whether depression-related deficits appear in non-memory abilities such as verbal or visuospatial functioning, assessed by means of neuropsychological tests.

The fact that effects of depression on cognition in AD are often not observed should be viewed in light of the fact that many individual-difference variables that are associated with cognitive functioning in normal aging have been shown to have less impact in AD. For example, effects of age, sex, and years of education on cognitive functioning are routinely observed in normal aging (e.g., Cullum et al., 2000; Inoye, Albert, Mohs, Sun, & Berkman, 1993; Wiederholt et al., 1993; for a review, see Bäckman, Small, & Wahlin, 2001), although their effects are negligible among demented persons (e.g., Bäckman et al., 1994; Buckwalter et al., 1993; Katzman et al., 1983; for a review see Bäckman et al., 1999). This may reflect the fact that the influence of various individual-difference variables on cognitive performance is overshadowed by the dementing process itself; depression is being yet another example. However, this issue has to be further examined during the transition from the preclinical to the clinical stages of the disease. Conceivably, effects of depression on cognitive performance in AD should be more likely to be observed in the very early (i.e., preclinical) phase of the dementia disease. In addition, cognitive domains other than episodic memory have to be more closely examined, including functions that are known to be affected later on in the disease process (e.g., verbal abilities, visuospatial skill, short-term memory; Almkvist & Bäckman, 1993; Grady et al., 1988; Small & Bäckman, 1998).

## RESEARCH OBJECTIVES

On the basis of the foregoing review, the general aims of this thesis were to examine the occurrence of depressive symptoms before the diagnosis of depression and AD, to study the effects of depression on cognitive functioning in old age, as well as to examine comorbidity effects of AD and depression on cognition in the preclinical and early clinical stages of AD.

All studies were based on epidemiological data from the Kungsholmen Project, which is a longitudinal survey focusing on aging and dementia in individuals who are 75 years and older. In the five papers that constitute the empirical basis of this thesis, the specific objectives were as follows:

**Study I**:     The major aim was to examine preclinical symptoms of MD both with regard to presence and severity, three years before the diagnosis of depression was rendered. A second goal was to determine whether cognitive impairment is a preclinical marker of MD.

**Study II**:     The objective was to investigate the occurrence of depressive symptoms, in terms of mood- or motivation-related symptoms, in the preclinical phase of AD, and to examine whether a potential elevation of depressive symptoms is related to subjective memory problems.

**Study III**:     The purpose was to assess potential comorbidity effects of AD and depression on episodic memory and short-term memory among prevalent cases of AD.

**Study IV**:     The goal was again to examine comorbidity effects of AD and depression on cognitive performance; in this instance, we focused on verbal and visuospatial skills among prevalent AD cases.

**Study V**:     The aim was, first, to investigate whether persons who were to be diagnosed with both depression and AD show larger cognitive deficits three years before diagnoses than those who were to be diagnosed with AD alone. In addition, we were interested in determining whether the cognitive decline from the preclinical phase to diagnosis was accelerated among persons who were to be diagnosed with both disorders compared to those who would receive an AD diagnosis.

# MATERIALS AND METHODS

## The Kungsholmen Project: Participants and Procedures

Data in this thesis were obtained from the Kungsholmen Project, a population-based longitudinal study in Stockholm, Sweden. For a detailed description of the project, the reader may consult Fratiglioni, Viitanen, Bäckman, Sandman, and Winblad (1992).

The general aim of the project is to study aging and dementia from a medical, psychological, and social perspective. The survey started in 1987 and ended in 2000. In total, five waves of data collection, at approximately 3-year intervals, have been completed.

Briefly, at baseline, completed between 1987-1989 all persons 75 years and older (born before 1912) living in the Kungsholmen parish in Stockholm were invited to participate in the study. The initial study population identified consisted of 2,368 persons, living in their own home or in institutions. Before the baseline assessment, 181 had died, 86 had moved, and 291 refused to participate, leaving a baseline population of 1,810 persons. The baseline assessment consisted of two phases. At Phase I, all persons were assessed with the Mini-Mental State Examination (MMSE; Folstein et al., 1975). The Phase I protocol also included a social interview, collection of vital parameters (e.g., functional status, blood pressure, height, weight), blood sampling, and assessment of drug use. Approximately 3 months after this screening, Phase II occurred. Here, all persons with cognitive impairment ($n$ =314), as determined by an MMSE scores of 24 or lower, and a sample of 354 comparison subjects (matched on age and sex) with MMSE scores higher than 24 were assessed with a complete medical examination including neurological and psychiatric assessments, social and family interviews, laboratory blood analyses, and a comprehensive cognitive test battery.

At the first follow-up, between 1991-1993, all subjects from the initial screening were invited back to participate, and of these 1099 persons were assessed. In the second follow-up, between 1994-1996, the sample hade been reduced to 680 persons. This thesis is based on data from baseline (Phase I and II), first follow-up, and second follow-up. In the third follow-up, between 1997-1998, the sample consisted of 421 persons, and in the last follow-up, between 1999-2000, the sample included 265 persons. At all follow-up assessments, the same protocol as used in Phase II, as described above, was used. A schematic description of the study design is presented in Figure 4.
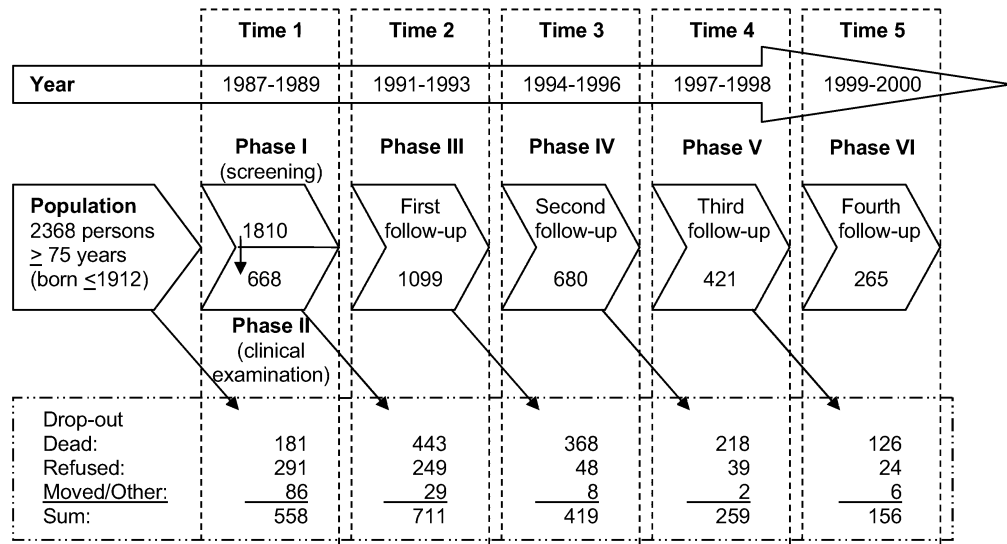
19

| | Time 1 | Time 2 | Time 3 | Time 4 | Time 5 |
|---|---|---|---|---|---|
| Year | 1987-1989 | 1991-1993 | 1994-1996 | 1997-1998 | 1999-2000 |
| | Phase I (screening) | Phase III | Phase IV | Phase V | Phase VI |
| Population 2368 persons ≥ 75 years (born ≤1912) | 1810 / 668 Phase II (clinical examination) | First follow-up 1099 | Second follow-up 680 | Third follow-up 421 | Fourth follow-up 265 |
| Drop-out Dead: | 181 | 443 | 368 | 218 | 126 |
| Refused: | 291 | 249 | 48 | 39 | 24 |
| Moved/Other: | 86 | 29 | 8 | 2 | 6 |
| Sum: | 558 | 711 | 419 | 259 | 156 |

**Figure 4**. Overview of the Study Design of the Kungsholmen Project

## Diagnostic Procedures

### Dementia

At baseline, participants with dementia were detected in two phases, as described earlier. In Phase I, the MMSE screening was used to detect suspected cases of dementia (MMSE < 24), and in Phase II a clinical examination was used to detect persons with dementia. The clinical dementia diagnosis was made according to DSM-III-R criteria (American Psychiatric Association, 1987). The diagnosis was made in multiple steps: In the first step, the physician who had examined the participants and reviewed their social and family history made a preliminary diagnosis. Step 2 involved a second preliminary diagnosis of all participants by a physician expert in dementia who had not been involved in the data collection. In Step 3, the two preliminary diagnoses were compared and cases with discordant diagnosis were reviewed again by the physicians to ascertain causes of agreement and disagreement. This eliminated most of the discordant diagnosis. In those cases where disagreement persisted, a supervising physician made the final diagnosis. The same diagnostic procedure was used at all follow-up occasions.

The criteria for diagnosis of AD were similar to those from the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD (McKhann et al., 1984).

**Depression**

Diagnoses of depression (i.e., major depressive episode or dysthymia) followed DSM-III-R or DSM-IV criteria (American Psychiatric Association, 1987; American Psychiatric Association, 1994). Diagnosis at baseline assessment was made according to DSM-III-R, whereas DSM-IV was used at the follow-up examinations. However, there are no significant differences between the two manuals with regard to the criteria for depression. Diagnoses were made by a physician expert in psychiatry and geriatrics on the basis of the results from the psychiatric examination that involved a structured interview using the Comprehensive Psychopathological Rating Scale (CPRS: Åsberg, Montgomery, Perris, Schalling, & Sedvall, 1978). When diagnosing major depressive syndrome, the criteria A, B, and E in the DSM-III-R and DSM-IV manuals were used. The criterion C was excluded because of difficulties in judging that the symptoms would cause clinically significant distress or impairments in social, occupational, or other important areas of functioning in this very old population. In addition, criterion D was eliminated because of difficulties in judging the etiology of depression in this age group (see Forsell et al., 1995).

## Measures

**Depressive Signs and Symptoms**

Information regarding specific depressive symptoms was derived from the CPRS (Åsberg et al., 1978). Each question was rated on a scale ranging from 0 to 6. According to established criteria, a score of 2 or more is indicative of pathology. Some of the CPRS items were transformed into the symptoms for MD stated in the DSM-IV after an evaluation of a psychiatrist.

In examining both the presence and severity of depressive symptoms (Study I) two sets of variables were created. When analyzing the presence of a symptom, we changed a score of 1 or lower to 0 (i.e., absence of a symptom), but because a score of 2 or higher indicated presence of a symptom, we changed it to 1. When focusing on severity of symptoms, we used the original scale ranging from 0 to 6.

On the basis of previous research (Bäckman, Hill, & Forsell, 1996; Forsell et al., 1993), the depressive symptoms in Study II and V were classified into two categories, reflecting either mood- or motivation-related symptomatology. The mood symptoms included: (a) dysphoria, (b) feelings of guilt, (c) suicidal thoughts/suicidal ideation, and (d) appetite disturbance. The motivation-related symptoms included: (a) lack of interest, (b) loss of energy, (c) concentration difficulties, and (d) psychomotor change. In factor analytic work (Forsell et al., 1993), the symptom sleep disturbance did not fit into any of the two categories of symptoms. Still, it was included in Study I, II, and V, as it is one of the symptoms stated in the criteria for diagnosis of MD. Further, the CPRS yields information about subjective memory complaints, which was analyzed in Study II.

**Cognitive Assessment**

To assess level of global cognitive functioning, a Swedish version of the MMSE was administered with a maximum score of 30. This is a brief screening test that covers various cognitive domains. The MMSE measures are: orientation to time, orientation to place, immediate

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word recall, attention, delayed word recall, naming, repetition, following commands, reading, writing, and design copy. The separate scores on each subscale range between 1 and 5.

The comprehensive cognitive battery was administered by trained psychologists. The test battery comprised a variety of psychometric tests and memory tasks, presented in two different test orders. Half of the subjects received the tests in one order, whereas the other half received the tests in reversed order. The subjects were tested individually and the total testing time was approximately 60 minutes. A brief description of the tasks used across the five studies is provided in Table 1.

**Table 1.** Cognitive Variables Examined as Dependent Variables Across Studies

| Study | Test | Function | Source |
|-------|------|----------|--------|
| I-V | MMSE | Global cognitive functioning | Folstein et al., (1975) |
| III | Digit Span Forward | Primary memory | Wechsler (1981) |
| III | Digit Span Backward | Primary memory, Working memory | Wechsler (1981) |
| III | Free Recall and Recognition of Words | Episodic memory | Wahlin et al., (1995) |
| IV | Block Design | Visuospatial ability, Constructional skills | Wechsler (1981) |
| IV | Clock Setting | Spatial orientation, Constructional skills | Christensen (1984) |
| IV | Category Fluency | Verbal skills, Semantic memory | Lezak (1995) |
| IV | Letter Fluency | Verbal skills, Semantic memory | Lezak (1995) |

**Episodic memory.** Episodic memory was assessed by means of free recall and recognition of word lists presented at fast (2sec/word) and slow (5sec/word) rates. In these tasks, two different word lists were used. Each list comprised 12 concrete nouns. The lists were comparable in terms of word length, frequency, concreteness, and imagery (Molander, 1984). Words were bimodally presented; they were presented visually printed on cards and read aloud simultaneously by the test leader. The subjects were instructed to remember the words for a later recall test. Immediately after presentation of the last word in each list, subjects were asked to free recall orally as many words as possible from the list, and the test leader recorded the responses. After each free recall test, subjects were, unexpectedly, given a yes-no recognition test. The target words were presented again

intermixed with an equal number of distractors. The resulting hits and false alarms were transformed into $d'$ scores. This is a discrimination index based on the proportion of hits and false alarms (Hochhaus, 1972). $d'$ scores range between -4.64 (lowest possible score) to +4.64 (highest possible score), with 0 representing chance performance. In order to obtain a measure of response bias, $C$ was calculated (Snodgrass & Corwin, 1988). $C$ is based on the $z$ -values for hits and false alarms and varies between -1.98 and +1.98. A measure of 0 indicates a neutral response bias, a positive value of C indicates a conservative bias (low tendency of guessing), and a negative value indicates a liberal bias (high tendency of guessing).

**Short-term memory**. STM was assessed by the digit span subtest from the WAIS-R (Wechsler, 1981). Both forward and backward repetition of digits was assessed according to standard procedures. The forward span test requires the person to repeat series of digits in the same order, starting with 3 digits and gradually increasing in length up to 9 digits. The rate of presentation was one digit per sec. In backward span, the person was asked to repeat the digits in reversed order. The easiest task consisted of 2 digits, whereas the most difficult involved 8 digits. Although both span tasks involve auditory attention and short-term memory (Lezak, 1995), they differ in that forward span assesses the ability to maintain information in short-term memory in a relative passive way, whereas backward span requires temporal reorganization of digits, and thus, poses additional demands on working memory (Baddeley, 1992).

**Verbal fluency**. Both category fluency and letter fluency were assessed. In both tests, individuals were given 1 minute to generate, orally, as many words as possible. For category fluency, subjects were instructed to generate as many exemplars of food as they could. In letter fluency, they were instructed to generate words beginning with the letters N and S, during 1 minute for each letter. Because of the high correlation between the two letter fluency tests ($r = .77$, $p < .001$), we used a composite score. In letter fluency, phonemic cues are used to guide word production, whereas category fluency relies heavily on the integrity of the semantic network (Monsch et al., 1992).

**Visuospatial ability**. Two measures of visuospatial ability were examined. First, a modified version of Block design, a subtest of the WAIS-R (Wechsler, 1981), was administered. The first two items were modified to be easier than in the original version in order to make sure that also severely demented cases could be graded. In total, the task consisted of seven designs, each involving four blocks. Standard procedures for administration were used and the Block design test was scored according to WAIS-R criteria. The maximum score was 24. However, the participant's performance was never interrupted and a second score without time limits was also obtained. Both scores have been included in the analyses: The number of correct answers within time limits (60 s; strict score) and the number of correct answers without time limits (lenient score).

The participants were also given the Clock drawing test according to standard procedures (Christensen, 1984). In this test, participants were asked to draw the hands on clock faces representing five indicated times. The Clock drawing test involved five circles with markings indicating number locations, although no numbers could be read. The times twelve o'clock, three o'clock, six o'clock, and nine o'clock had heavier markings. For each circle, the person was asked to indicate a particular time by drawing the hands on each clock. The times to be drawn were two o'clock, five o'clock, three o'clock, ten-forty-five, and seven-fifteen. The latter two clock times were read ten-forty-five and not quarter to eleven, and seven-fifteen not quarter past seven.

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**Background Variables**

As noted earlier in the text, many background factors are important to control for when investigating cognitive functioning as well as depression (for reviews, see Bäckman et al., 1999; Fahlander et al., 2000; NIH Consensus Conference, 1992). In the following, the key background variables assessed in the present research are described.

**Demographic factors**. Age, sex, and years of education were compared across diagnostic groups in all studies.

**Functional ability**. Study I, II, and IV included information about the person's functional ability, as measured by Katz Activities of Daily Living (ADL) index (Katz et al., 1963). This measure inquires about the person's ability to perform tasks such as bathing, dressing, feeding, transferring, going to the toilette, and continence. The score ranges from 1 (independent) to 7 (dependent).

**Diseases**. Study I, II, and V obtained information about history of diseases. In Study I and II, information about utilization of care in relation to psychiatric diseases and treatment for these diseases was gathered. Study I also included disease data obtained from the clinical examination at phase II (i.e., diabetes, high blood pressure, cardiac insufficiency, angina pectoris, arthritis/rheumatism, ischemic attacks, autoimmune disease, cataract, glaucoma, cancer, chronic pain). In study V, information about a number of somatic disorders was analyzed more thoroughly. All diseases were ascertained by reviewing hospital discharge diagnosis through the Stockholm Computerized Inpatient Register System. This register includes main diagnoses and up to five secondary diagnoses from all occasions when a person has been admitted to a hospital as an in-patient. Disease diagnoses were based on the International Classification of Disease, 9th edition (ICD-9, World Health Organization, 1987). The specific diseases examined were blood diseases (ICD-9: 280-289, e.g., iron deficiency anemia, other deficiency anemia), cancer (ICD-9: 140-208, 230-239, e.g., malignant neoplasm of large intestine, malignant neoplasm of breast), cardiovascular diseases (ICD-9: 390-429, e.g., myocardial insufficiency, angina pectoris), cerebrovascular diseases (ICD-9: 430-438, e.g., transient cerebral ischemia, cerebral embolism), diseases of arteries (ICD-9: 440-48, e.g., arteriosclerosis, aneurysm), other diseases in the circulatory system (ICD-9: 450-58, e.g., pulmonary embolism, infarction) digestive diseases (ICD-9: 530-579, e.g., stomach ulcer, intestinal obstruction), endocrine diseases (ICD-9: 240-279, e.g., diabetes, amyloidosis), genito-urinary diseases (ICD-9: 580-629, e.g., cystitis, urinary tract infection), infectious disease (ICD-9: 0-139, e.g., intestinal infections, septicemia) mental diseases (ICD-9: 291-315, excluding dementia, e.g., psychosis associated with cerebral condition, transient situational disturbances), musculoskeletal diseases (ICD-9: 710-738, e.g., rheumatoid arthritis, arthritis), nervous system diseases (ICD-9: 320-389, e.g., Parkinson's disease, eye diseases), and respiratory diseases (ICD-9: 460-519, e.g., pneumonia, asthma).

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**Ethical Considerations**

All participants were fully informed about the aim of the Kungsholmen Project and that they had the right to refuse participation at any time. When a person was suspected to be demented, next-of-kin was asked for consent after they had been fully informed about participation and the aim of the survey. All data are confidential, unidentified, and kept in fire safe archives. The Kungsholmen Project is approved by the ethical committee at the Karolinska Institute: Dno. 87:148; Dno. 90:251; Dno. 94:122; Dno. 01:020.

# RESULTS

Table 2 provides an overview of the samples used across the five studies with regard to demographic characteristics and MMSE performance. As can be seen, all studies involved very old adults with comparable educational background. In addition, the level of global cognitive functioning varied across subject groups in the expected direction.

**Table 2**. Subject Characteristics Across Study Samples

|  | % female | Age | | Years of education | | MMSE | |
|---|---|---|---|---|---|---|---|
|  |  | *M* | *SD* | *M* | *SD* | *M* | *SD* |
| Study I |  |  |  |  |  |  |  |
| Incident MD | 90 | 84.6 | 5.1 | 9.8 | 3.5 | 26.8 | 1.7 |
| Normal old | 79 | 83.1 | 4.8 | 9.0 | 3.1 | 28.0 | 1.6 |
| Study II |  |  |  |  |  |  |  |
| Incident AD | 91 | 85.5 | 5.0 | 8.6 | 2.6 | 25.7 | 1.5 |
| Normal old | 80 | 83.2 | 4.8 | 9.0 | 3.1 | 27.9 | 1.6 |
| Study III & IV |  |  |  |  |  |  |  |
| AD/D | 78 | 84.0 | 4.2 | 9.8 | 2.3 | 19.1 | 5.8 |
| AD | 76 | 83.9 | 5.3 | 8.0 | 2.4 | 19.7 | 3.4 |
| Normal old | 81 | 84.0 | 5.1 | 8.8 | 2.7 | 27.7 | 1.5 |
| Study V |  |  |  |  |  |  |  |
| Incident AD/D | 100 | 83.5 | 4.5 | 9.4 | 2.3 | 24.2 | 2.8 |
| Incident AD | 82 | 84.9 | 4.3 | 8.3 | 2.4 | 25.2 | 4.3 |
| Normal old | 79 | 85.1 | 4.5 | 9.0 | 3.3 | 27.4 | 2.0 |

In the following, the five empirical studies conducted as apart of this thesis are discussed.

## Study I

The major aim of this study was to examine potential preclinical depressive symptoms of MD, in terms of presence and severity, three years before the clinical diagnosis was rendered. A second focus was to examine whether cognitive deficits are present three years before the depression diagnosis.

We compared individuals who were non-depressed at baseline assessment but received an MD diagnosis three years later ($n = 10$) with a healthy non-depressed control group ($n = 175$) with regard to depressive signs and symptoms and global cognitive functioning measured by the MMSE. As to the latter, we examined the total score as well as specific MMSE items.

In addition to age, sex, and years of education, information about the subject's functional ability and a number of chronic disorders was gathered. The two groups were indistinguishable on all these variables except for number of somatic disorders. Those persons who were to be diagnosed with MD three years later had a higher number of somatic diseases. Because diseases may be related to both depression and cognitive deficits (Bäckman et al., 1999; Fahlander et al, 2000; NIH Consensus Conference, 1992), somatic disorders were controlled for in the analyses. One inherent problem when studying preclinical indicators of a disease in population-based studies is the uncertainty concerning the exact time of the disease onset. Therefore, we obtained information regarding previous psychiatric history, anti-depressant drug use, and contact with health care professionals for psychiatric symptoms. None of the incident depressed subjects had a previous history of depression or any other psychiatric disorder, none had been in contact with primary or special care for psychiatric treatment, and none had received anti-depressant treatment as assessed at the follow-up examination.

The results revealed that those who were depressed at follow-up differed preclinically from those who remained non-depressed in terms of both presence and severity of symptoms. The incident depressives had more evident and severe symptoms than their non-depressed counterparts. Specifically, group differences were seen for both presence and severity of dysphoria and appetite disturbance. In addition, the incident depressed exhibited more severe lack of interest and psychomotor disturbance. The depressed subjects also had poorer cognitive performance in terms of lower MMSE total score and on the orientation to time item. The source of impairment for this specific MMSE item may be related to apathy or lack of motivation in the testing situation, which may be a contributing factor for recalling less information about their daily life.

Thus, Study I suggested that there are preclinical markers for people who will become depressed in old age after a three-year interval. The findings of elevated symptoms three years before the diagnosis of depression coupled with no history of seeking help for psychiatric problems indicate a relatively long preclinical period of MD in old age. Thus, the course of depression in elderly persons may be more chronic than acute in nature. A lengthy development may be more common among very old adults than in younger adults where the disease normally develops over days to week according to DSM-IV criteria.

## Study II

The general objective of Study II was to examine depressive symptoms in the preclinical phase of AD three years before the diagnosis was rendered. We compared incident AD cases (*n* =34) and non-demented subjects (*n* = 188) on baseline mood- (i.e., dysphoria, appetite disturbance, feelings of guilt, thoughts of death) and motivation-related (i.e., lack of interest, concentration difficulties, loss of energy, psychomotor disturbance) symptoms of depression, and assessed whether depressive symptoms in preclinical AD were related to self-perceived memory problems. This was done under the assumption that if mood-related symptoms would dominate in preclinical AD, this may reflect, in part, emotional reactions to self-perceived cognitive deficits, and possible insight into the emerging disease process. On the other hand, if motivation-related symptoms were to dominate, this may be independent of subjective cognitive problems, and rather reflect disease-related changes in brain regions critical to allocation of attentional energy.

Background information including age, sex, education, functional ability (Katz ADL), and global cognitive functioning (MMSE) was analyzed. The results indicated that the incident AD cases were older, had lower MMSE scores, and were more functionally impaired than the non-demented control group at baseline. It is well established that AD has a rather long preclinical period during which deficits are present (Albert et al., 2001; Bäckman, Small, & Fratiglioni, 2001; Chen et al., 2001; Lambon-Ralph et al., 2003); therefore, the poorer cognitive performance and the functional impairment did not come as a surprise. In addition, as in Study I, information was gathered at follow-up regarding prior psychiatric disorders, contact with health care professionals for psychiatric symptoms, and anti-depressant drug treatment. None of the AD cases had a previous history of depression or other psychiatric disorder.

The main finding of this study was that persons who would develop AD across the follow-up interval exhibited an elevation of depressive symptoms at baseline assessment compared to those who remained non-demented. We found a dominance of motivation-related symptoms (e.g., lack of interest, loss of energy, concentration difficulties) over mood-related symptoms of depression in preclinical AD. This association remained after adjusting for demographic factors (age, sex, and education) and subjective memory complaints. The chief conclusion from Study II was that depressive symptoms are elevated preclinically in AD, and that this elevation is not merely a byproduct of self-perceived cognitive difficulties. Therefore, it was suggested that depressive symptoms might be a part of the pathological processes in AD.

## Study III

The aim of Study III was to investigate if depressive disorders exacerbate episodic memory deficits in prevalent cases of AD. We compared normal old adults (controls, $n = 296$), AD cases (AD, $n = 45$), and persons with AD and depression (AD/D, $n = 9$) on tasks measuring episodic memory and short-term memory. Episodic memory was assessed with free recall and recognition of rapidly and slowly presented words. Short-term memory was assessed using digit span forward and backward. The two AD groups were mildly to moderately demented.

Several factors have to be considered when examining the effects of depression on memory performance. First, a variety of individual-difference variables have been found to influence episodic memory in normal aging (e.g., age, sex and years of education). No differences between the two AD groups were observed on these variables. Further, when studying comorbidity effects of AD and depression on cognitive functioning, it is critical to control for dementia severity. However, there are methodological challenges when matching these groups on dementia severity by using some global measure of cognitive functioning (i.e., MMSE), given that the dependent measure of interest (i.e., episodic memory) is related to global cognitive functioning. Therefore, we computed an additional measure of dementia severity (i.e., disease duration) by subtracting the age at onset, as reported by the subject and/or an informant, from the age of the subject at the time of testing. The AD/D group had slightly longer disease duration but did not differ reliably from the non-depressed AD group. Further, before matching the two AD groups on dementia severity using the MMSE score, we corrected the scores for the delayed recall item, because our main outcome measures were episodic memory tasks.

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There was no effect of depression in AD on performance in any episodic memory task. Further, with the exception of performance on digit span forward, the control group outperformed the two AD groups, reflecting clear dementia-related episodic memory deficits in both groups. In free recall, only the normal control group showed gains as task pacing decreased. However, all groups benefited from more study time in recognition. This suggests that AD cases with and without depression have similar deficits in the ability to utilize more study time for remembering when memory are assessed with free recall but not in recognition. With the provision of cues in the recognition task, the memory traces were recovered more easily, and effects of more study time could be observed. This finding indicates that individuals with AD need cognitive support both at encoding and retrieval to show memory enhancement. Given that the lack of effect of depression on episodic memory in AD may be due to an overlap in motivation-related symptoms (e.g., loss of energy, concentration difficulties) among AD and AD/D cases, all analyses were repeated with a modified AD group after removing all cases with at least one motivation-related symptom. However, all results remained unchanged.

In conclusion, AD was associated with deficits in episodic memory and working memory (i.e., digit span backward), although primary memory (i.e., digit span forward) was unaffected. Depression did not exacerbate AD-related memory deficits. Thus, the effect of depression may be overshadowed by the neurodegenerative process of AD. As such, depression seems to resemble many other individual-difference variables (e.g., age, sex, education) that are important to cognitive functioning in normal aging, but have limited or no effect in the presence of AD.

## Study IV

Study IV was a continuation of Study III. The objective was to examine whether depression has a negative influence on AD-related deficits in cognitive domains other than episodic memory, such as verbal ability and visuospatial skill. As with episodic memory, these cognitive functions have been found to be negatively affected by depression among non-demented persons (Abas et al., 1990; Emery & Breslau, 1989; Veiel, 1997). There is also some evidence in research on non-demented older adults that verbal skills are more compromised in depression than episodic memory (Emery & Breslau, 1989; Geffen, Bate, Wright, Rozenbilds, & Geffen, 1993). This leaves open the possibility that effects of depression in AD may be more easily observed in verbal and visuospatial tasks than in episodic memory tasks. In addition, given the fact that the largest cognitive deficit in early AD is seen in episodic memory the room for further deterioration as a function of depression may be more restricted in episodic memory than in other cognitive domains. As a result, depression may affect verbal and visuospatial functions among prevalent cases of AD in a mild to moderate stage of the disease. The sample was the same as in Study III, including three groups: AD/D ($n$ = 9), AD ($n$ = 45), and a healthy non-demented and non-depressed control group ($n$ = 296). Two measures of verbal fluency (i.e., letter and category fluency) were used to assess verbal ability. Visuospatial skill was assessed with Block design (under paced and self-paced conditions) and a clock-setting task.

Except for the Katz ADL index, the data pertaining to the background variables were, for obvious reasons, identical to those reported under Study III (see above). There were no differences between the two AD groups with respect to these background variables but in terms of functional

ability both demented groups were judged to be partially functionally dependent, whereas the healthy control group was functionally independent.

The control group outperformed both AD groups across all cognitive tasks. Again, depression did not worsen the cognitive dysfunction in AD: The two demented groups were indistinguishable across all verbal and visuospatial measures. Both AD groups showed relatively poorer performance on category fluency compared to letter fluency, possibly reflecting greater demands on the integrity of the semantic network in the case of category fluency. Although the two AD groups showed clear deficits under both paced and self-paced conditions in the Block design task, an interesting observation was that these groups showed performance increments of the same magnitude as the healthy control group when no time limits were imposed. As with the episodic memory data in Study III, this finding indicates that mild to moderate AD patients with or without depression still possess some cognitive reserve capacity, a potential for improving performance under more supportive conditions.

The findings of Study IV provide further support for the view that depression does not aggravate AD-related cognitive problems, likely reflecting that the influence of this condition, as true for many other individual-difference variables, is overshadowed by the dementing disease.

## Study V

In Study V, we examined whether persons who were to be diagnosed with both AD and depression showed greater cognitive deficits three years before diagnoses than those who were to be diagnosed with AD alone. Although such comorbidity effects have been difficult to demonstrate among prevalent cases of AD (Study III and IV), they may be more easily observed when the process of dementia has not progressed to a point at which the influence of other variables, such as depression, is absorbed. Further, to the extent that depression would exacerbate preclinical cognitive deficits in AD, we were interested in examining whether such effects could be linked to specific depressive symptoms, in terms of mood- or motivation-related symptomatology. In previous research, motivation-related symptoms have been found to be more cognitively loaded, and been linked to the individual's basic processing resources (Bäckman, Hassing et al., 1996, Bäckman, Hill et al., 1996). Finally, we investigated whether rate of cognitive decline during the transition from the preclinical phase to clinical diagnosis was accelerated among persons who were to be diagnosed with both depression and AD compared to those who would receive an AD diagnosis. Three groups were examined over a 3-year follow-up interval consisting of subjects with AD/D ($n = 13$), AD ($n = 109$), and a normal healthy control group ($n = 179$). The three groups were compared both preclinically and at the time of diagnoses on global cognitive functioning (i.e., MMSE) and the occurrence of depressive symptoms.

There were no differences in demographic factors (e.g., age, sex, education) across the diagnostic groups. However, we also wanted to make sure that the two AD groups were comparable in terms of number of somatic health conditions. This is of particular importance in the current context as depression may be associated with various somatic diseases and many elderly adults tend to report more somatic complaints rather than depressed mood, which may lead to an underestimation of depression in old age (Crum et al., 1994; NIH Consensus Conference, 1992). Thus, we examined all available diseases that occurred from baseline to follow-up using the

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Stockholm Inpatient Register. The two AD groups were found to have more diseases than the controls, but the demented groups did not differ from each other for any of the specific diseases. Thus, these findings indicate that the two AD groups were comparable in terms of the presence of a number of somatic diseases that are known to be critical to cognitive functioning and the occurrence of depression in aging.

As expected, the results revealed clear AD-related cognitive deficits preclinically on MMSE total score as well as for specific items (i.e., orientation to time, orientation to place, delayed memory, repetition, follow commands, design copy), which were exacerbated at the time of diagnosis. In addition, we found minor depression-related deficits on cognitive functioning in preclinical AD, which were linked to an elevation of depressive symptoms. Specifically, persons who would develop both AD and depression scored lower on the MMSE items follow commands, reading, and writing. The depressive symptoms for which the depressed AD group showed an elevation at baseline (e.g., dysphoria, loss of energy) may make it difficult to carry out tasks that individuals with no such symptoms complete relatively automatically, because of lack of motivation in the testing situation. The fact that the two incident AD groups differed at baseline indicates that there is some room for individual difference-variables (i.e., depressive symptoms) to influence cognitive functioning in preclinical AD. However, depression was not associated with greater cognitive decline over the three-year follow-up period. Thus, although depressive symptoms may result in slight cognitive deficits in preclinical AD, at the time of diagnosis these effects seem to be absorbed by the neurodegenerative process.

## GENERAL DISCUSSION

### Depression in Elderly Persons

Study I examined the occurrence of baseline depressive symptoms and cognitive impairment in persons who were incident depressed or non-depressed at the follow-up examination three years later. The results showed that individuals who would become depressed had elevated depressive symptoms preclinically, both in terms of presence (i.e., dysphoria, appetite disturbance) and severity (i.e., dysphoria, appetite disturbance, lack of interest, psychomotor disturbance) of symptoms. It is interesting to note that both dysphoria and lack of interest, which are the main symptoms required for a diagnosis of depression, showed elevation already three years before diagnosis. Although the symptoms have to reach a pathological level (in this case a score of two or higher on the CPRS) in order to meet the diagnostic criteria, they are still elevated preclinically. Thus, in order to obtain an accurate portrayal of early harbingers of depression in old age, it may be important to focus on both the presence and severity of symptoms. This is of particular relevance, given that other research has found an increased risk to develop a full-blown depression among those who exhibit some depressive symptoms (Jorm, 1995; Kivelä et al., 1996).

Given that we found elevated symptoms three years before the diagnosis of depression, there are reasons to believe that depression in old age is more chronic than acute in nature. That the development of depression may take many years contrasts to the relatively short clinical onset expected in younger adults. In DSM-IV, it is stated that symptoms of a major depressive episode "usually develops over days to weeks" (p. 325). However, there are some issues to consider when arguing that depression tends to be more chronic in old age. First, depression is a disorder known to fluctuate over time (DSM-IV; American Psychiatric Association, 1994). Second, it is difficult to control for disease onset that may have occurred relatively shortly after baseline assessment given the fixed follow-up intervals. In order to address the disease onset issue in Study I, we controlled for psychiatric health status from baseline assessment until the follow-up examination. None of the depressed subjects had a previous history of depression or any other psychiatric disorder, and none had received treatment for a psychiatric condition. This strengthens our belief that depression in old age is underrecognized and more chronic in nature. Note that similar conclusions have been made in other studies (Fröjdh et al., 2003; Sharma et al., 1998). Standard diagnostic instruments (i.e., DSM-IV) may have to take this point into account when describing the course of depression in old age.

A second aim of Study I was to examine cognitive functioning as a preclinical marker in old age depression. The results revealed that depressive symptoms before the MD diagnosis had an effect on cognitive functioning. Persons who would become depressed within a 3-year period scored lower on the MMSE total score and showed poorer performance on the item orientation to time. There was also a tendency for a poorer performance on the item delayed word recall ($p = .07$). The source of impairment for the lower score on the item orientation to time may be related to apathy or lack of motivation in the testing situation. Comparing the non-depressed group and the incident MD groups, we found the depressed subjects to exhibit more lack of interest that may

result in recalling less information about their everyday life. To make a correct answer on the orientation to time item may require more intrinsic motivation than other MMSE tasks that provide more structure (e.g., design copy). Although the effects of elevated symptoms of depression on global cognitive functioning were relatively minor, it has to be kept in mind that we examined individuals in a preclinical phase of depression. Even in studies targeting clinically depressed persons, there have been difficulties in finding distinct patterns of cognitive deficits (Feehan et al, 1991; King et al., 1991; Sweeny, Weltzer, Stokes, & Kocsis, 1989). Further, in a meta-analysis Burt et al. (1995) found the relationship between depression and memory impairment to decrease in magnitude with advancing age (see also Kindermann & Brown, 1997). Further, as alluded to, motivation-related symptoms of depression have been found to be more cognitively loaded and linked to the individual's basic processing resources, such as the ability to sustain attention on a task while closing out irrelevant information (Bäckman, Hassing et al., 1996; Bäckman, Hill et al., 1996). It has been demonstrated that motivation-related, but not mood-related, symptoms of depression are related to cognitive performance in clinically non-depressed and non-demented elderly people (Bäckman, Hill et al., 1996). In this study we found that the incident depressed subjects complained more over mood-related symptoms, which thus is in line with the relatively small cognitive deficits.

At any rate, we found that individuals who were to be depressed after a 3-year follow-up interval were more cognitively affected compared to healthy controls at baseline. Therefore, when screening for or diagnosing depression in old age, it may be of clinical relevance to screen for cognitive dysfunction in order to evaluate the degree of impact of the depressive disorder.

### Depressive Symptoms in the Preclinical Phase of MD and AD

Sometimes it is hard to differentiate between depression and early dementia because symptoms are overlapping, both in terms of patterns of cognitive dysfunction and depressive symptoms (Christensen et al., 1997; Forsell, et al., 1993; Rubin, 1990).

Both Study I and II examined preclinical signs and symptoms of depression. Compared to normal controls, both MD and AD persons showed an elevation of depressive symptoms in the preclinical period of the diseases. However, the symptom distributions differed somewhat across diagnostic groups in terms of severity of mood- compared to motivation-related symptoms (see Figure 5). Comparing the results in these two studies, it appears that there is a predominance of mood-related symptoms in preclinical MD (e.g., dysphoria, appetite disturbance), whereas elevated depressive symptoms in the preclinical phase of AD are more motivation-related (e.g., lack of interest, concentration difficulties, loss of energy).
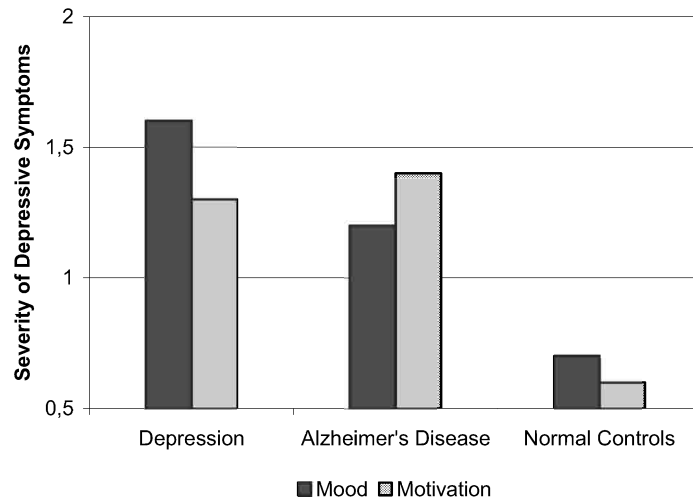
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**Figure 5.** Preclinical Depressive Symptomatology Across Diagnostic Groups

Considering the relationship of depressive symptomatology to cognitive functioning, some researchers have argued that elevated symptoms of depression in early AD may reflect insight into the cognitive problems and the emerging disease process (e.g., Migliorelli et al., 1995). The present findings did not support this contention. Specifically, in Study II, we examined the role of subjective memory complaints and the patterns of depressive symptomatology (i.e., mood- vs. motivation-related symptoms). Although the incident AD cases complained more about memory problems than the controls, the relationship between depressive symptoms and diagnostic status three years later remained unchanged, regardless of whether subjective memory complaints were controlled for statistically. Moreover, the pattern of findings (see Figure 5) indicated that the elevation in the preclinical phase of AD were more pronounced for motivation-related symptoms than mood-related symptoms, the latter category typically associated with depression (e.g., dysphoria). Thus, these symptoms may reflect early signs of an emerging dementing disease rather than being reactive (see also Ballard et al., 1993; Cummings et al., 1995; Verhey et al., 1993). Further, to the extent that motivation-related symptoms (e.g., lack of interest, concentration difficulties) are common in the normal older population (Blazer, 1989; Girling, et al., 1995; Livingstone, Hawkins, Graham, Blizard, & Mann, 1990), these symptoms may be easily overlooked as preclinical markers in AD.

When examining persons who were to develop both AD and depression in Study V, we found elevated depressive symptoms preclinically both with regard to mood- and motivation-related symptoms. Considering the findings in Study I and following the line of reasoning above, this may reflect that these individuals were experiencing the emergence of two parallel disease processes. However, note that persons who were to develop AD without depression in this study did not differ significantly from the controls in terms of depressive symptoms, although there was a

tendency in the direction of an elevation for the AD group across many of the symptoms (e.g., loss of energy, appetite disturbance, thoughts of death). These somewhat conflicting results may be due to the use of different exclusion criteria in Study II and Study V. In support of the data in Study II, other research has also found motivation-related symptoms to be more frequent than mood-related symptoms in the preclinical and very early clinical stages of AD (Li, Meyer, & Thornby, 2001; Rubin, 1990). However, further research is needed to better characterize different profiles of depressive symptoms in the development of MD and AD.

## Lack of Depression-Related Deficits on Cognitive Functioning in AD

Although there are depression-related deficits across in multiple cognitive domains in normal aging (Abas et al., 1990: Bäckman & Forsell, 1994, Ravnkilde et al., 2002; Veiel, 1997), the effect of depression of cognitive performance was negligible among prevalent cases of AD (mild to moderate stages) in Study III, IV, and V. Thus, it was concluded that depression does not exacerbate AD-related deficits in episodic memory, short-term memory, verbal fluency, visuospatial skills, or global cognitive functioning. Although several methodological issues were considered matching depressed and non-depressed AD cases on dementia severity (i.e., adjusting the MMSE total score for episodic memory, age of onset, duration of disease) that may have contributed to the negative findings in previous studies (Pearson et al., 1989; Bäckman, Hassing, et al., 1996), we found no effects of depression. To the extent that AD cases already suffer from cognitive deficits related to motivational and attentional symptoms of depression as a result of the neurodegenerative process itself (Baddeley, 1986; Baddeley et al., 1986; Hartlage et al., 1993), null effects should, indeed, come as no surprise. In Study III, we were considering the possibility of overlapping of symptoms between the two diseases. However, additional analysis adjusting for motivation-related symptoms did not alter the findings of a lack of effect of depression on episodic memory performance. Perhaps other more specific cognitive tests of attention and executive functioning would clarify whether the negative findings are due to the fact that the cognitive repercussions of depression are already accounted for by the degenerative process. In any event, these results replicate earlier findings focusing on episodic memory (e.g., Bäckman, Hassing et al., 1996). In addition, our results extend prior research to other cognitive functions, such as verbal ability, visuospatial skill, and short-term memory. Thus, depression, like many other individual-difference variables, seems to be of minor importance to a variety of higher-order cognitive functions in AD.

Although depression does not seem to affect cognitive functioning among prevalent cases of AD, it is important to keep in mind that this disease is affecting general psychological functioning and well being in dementia (Gonzales-Salvador, et al., 2000; Lyketsos et al., 1997; Payne et al., 1997), as well as increases caregiver burden (Gonzales-Salvador et al., 1999). Thus, the present findings should not be taken to mean that it is unnecessary to evaluate and treat depression in dementia. However, treating depression in dementia may not be expected to result in cognitive improvement.

### Depression-Related Influence on Cognition in Preclinical AD

With regard to the lack of effects of depression on cognition in AD (Study III and IV), we first have to consider the fact that these effects decrease with advancing age among non-demented persons (Burt et al., 1995; Kindermann & Brown, 1997). Thus, the room for depression to exert an influence on cognition in AD in these high ages is somewhat limited. However, given that the onset and progression of dementia are gradual, it is not inconceivable that individual-difference variables (e.g., depression) may influence cognitive functioning preclinically. It may be more likely to find associations between various subject characteristics and cognitive functioning when the dementia disease has not yet progressed to a point at which various factors are overshadowed by the pathological processes. In Study V, we followed persons over a 3-year interval, from the preclinical phase until diagnoses. In addition to results indicating preclinical AD-related deficits, we found depression-related deficits prior to the AD diagnosis, in terms of poorer performance on the MMSE items follow commands, reading, and writing. It has been hypothesized that cognitive deficits in depression should be more pronounced in tasks requiring effortful processing (e.g., the MMSE item delayed memory) compared to more automatically executed tasks (e.g., reading, writing). Obviously, our findings do not support this view. Rather, the data are consistent with meta-analytic evidence of Christensen et al. (1997) that depression-related cognitive deficits may occur also in overlearned cognitive tasks. The current findings extend this observation to individuals who are in the preclinical phase of both depression and AD.

To summarize the findings from Study V, there seems to be room for individual-difference variables to aggravate cognitive deficits in the preclinical phase of AD, which is a novel finding. On the other hand, we could not demonstrate depression to cause accelerated cognitive decline during the transition to clinical AD. This suggests that at the time of diagnosis, the dementia disease processes may have reached a level where it is difficult for other conditions to further exacerbate the cognitive problems.

### Validity of the Findings

The external validity of the results in the five studies can be considered to be high. The present findings are derived from studies using population-based samples including all persons in a certain geographical area. The age- and gender distributions were comparable to other parts of Stockholm. In addition, the dropout rates have been found to be very low in the Kungsholmen Project (von Strauss et al., 1999). Therefore, the results may generalize to Swedish urban populations aged 75 years and older and, possibly, to other older urban populations in western societies. However, other issues concerning the validity of the findings in this thesis should be addressed. In the following, I discuss five such issues, namely sample size, representativness of samples, length of follow-up intervals, aggregation of depressive disorders, and measurement properties of the cognitive tasks.

### Sample Sizes

Across all studies that examined depression there is a problem with small sample sizes (including only 9 up to 13 cases), which clearly affects the power to detect statistically significant differences between the groups. Toward this end, it has repeatedly been shown that depressed

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subjects constitute a problematic group in epidemiological studies, that they tend to dropout more often and to have a higher frequency of mortality than their non-depressed counterparts (Schultz et al., 2002; Unütser et al., 2002). In the Kungsholmen project, there were 33 non-demented subjects that had a diagnosis of MD at baseline (Phase II), at first follow-up the number had decreased to 10 cases, and at the second follow-up the number had further decreased to 6 persons. In addition, when depressed subjects do participate they often have incomplete cognitive data because of lack of motivation in the testing situation. Thus, in population-based research, even in a relatively large study like the Kungsholmen Project, it may, unfortunately, not be realistic to obtain meaningful cognitive data on a large number of depressed persons.

## Representativness of Samples

In both Study I and II, a number of persons were excluded. For example, in Study I we excluded persons with dementia, Parkinson's disease, history of stroke, psychiatric disorders, and those with an MMSE score below 24. These exclusions were made in order to minimize the risk of including persons who suffer from somatic diseases associated with depression, as well as persons who may have been in a preclinical phase of dementia. In addition, as we were interested in determining the influence of depression on cognitive functioning in aging and dementia, we thought it was important to minimize the influence of concomitant condition on cognitive performance. This approach can be questioned given that these conditions are frequently occurring in the elderly population. Thus, the exclusion criteria may jeopardize the external validity. However, the study objective was to examine depression in its purest form and we wanted to avoid the risk of depressive symptoms being caused by conditions other than depression. Thus, by excluding persons on the basis of the above criteria we likely increased the internal validity of the results.

## The Time Frame of Follow-Up Intervals

Obviously, the suitable time frame of follow-up periods is an issue of paramount importance in studying the development of two rather different disorders such as depression and AD. Depression is a disorder that may develop over days to weeks, whereas AD has a long preclinical period. The Kungsholmen Project was designed to study aging and dementia with follow-up periods every third year, which may be reasonable from an AD perspective. On the other hand, in depression, a disease that is known to fluctuate over time, the same follow-up period may increase the risk of subjects being undetected, as well as of drawing incorrect conclusions about depression being a chronic disorder in old age. In Study I, we tried to minimize the latter possibility by including information about previous care for psychiatric problems and anti-depressant treatment. However, the former problem needs to be addressed by employing shorter follow-up periods.

## Aggregation of Depressive Disorders

Another potential weakness that should be acknowledged is that we grouped persons with MD and dysthymia into one diagnostic category in order to increase the number of depressed subjects in Study III-V. Thus, the inclusion of dysthymic subjects may have resulted in symptoms not being severe enough to cause an exacerbation of the cognitive deficits in AD. However, research indicates that dysthymia may have negative repercussions for cognitive functioning

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(Marshall, Forstot, Callies, Peterson, & Schenk, 1997; Yee & Miller, 1994). Moreover, previous work has demonstrated null effects of depression on cognitive performance in AD when the sample of AD/D subjects was restricted to MD only (Bäckman, Hassing et al., 1996).

**Floor and Ceiling Effects in the Cognitive Measures**

In Study I and V, only the MMSE was used to examine cognitive functioning because of too much missing data among the incident depressed subjects on the comprehensive cognitive battery. The MMSE covers most but not all cognitive domains. In addition, the separate cognitive domains are not measured in an extensive way and the variability in scores on the subtests is limited. Many cognitive domains (verbal and visuospatial skills) are assessed with one question only (i.e., repetition, reading, writing, design copy) resulting in a score that can be either one or zero and the risk of floor or ceiling effects is difficult to avoid. The risk of ceiling effects may be especially pertinent among persons who are relatively intact cognitively, which in part, may explain the rather small differences between the preclinical MD persons and the controls in Study I. In Study V, the MMSE was used to examine preclinical depression-related deficits on cognitive functioning among persons who were going to develop both AD and depression. In this study, this potential weakness may not be considered to be as critical as in Study I, because the AD groups were expected to be more impaired cognitively.

The opposite problem is present for prevalent AD cases in heavily demanding cognitive tasks (e.g., episodic memory, fluid intelligence). In particular, the free recall data in Study III are obviously close to the floor for the AD and AD/D groups. This limits the possibility of finding group differences. At the same time, the data indicate that mildly to moderately demented AD patients with or without depression perform at a very low level in tasks routinely used to evaluate episodic memory functioning.

## CONCLUSIONS

The key findings from the five studies included in this thesis can be summarized as follows:

1. There seem to be preclinical markers for MD in old age three years before diagnosis, both in terms of an elevation of depressive symptoms and regarding global cognitive functioning.

2. Depressive symptoms, particularly motivation-related symptoms, are elevated in the preclinical phase of AD. This elevation is not merely a byproduct of self-perceived cognitive deficits, but may rather reflect the emerging neurodegenerative process.

3. Depression does not further exacerbate AD-related cognitive deficits in global cognitive functioning, short-term memory, episodic memory, verbal fluency, or visuospatial skill among prevalent cases in a mild to moderate stage. Thus, already at an early clinical stage of AD, the neurodegenerative processes appear to overshadow the impact of depression, although this condition is associated with cognitive deficits in normal aging.

4. In the preclinical stage of AD, there may still be some room for individual-difference variables (e.g., depressive symptoms) to cause further cognitive impairment. However, a diagnosis of depression does not result in faster cognitive decline during the transition from preclinical AD to the time of diagnosis.

## RELEVANCE AND IMPLICATIONS

Dementia and depression are common disorders in elderly people. Both disorders cause impairment in various cognitive, behavioral, and functional domains, and they are costly for society. Thus, increased knowledge about these two disorders should be helpful in the planning for interventions and prevention.

The bulk of research in this field is based on clinical samples. However, population-based studies have an advantage compared to convenience samples with regard to the generalizability of the findings. Studies on representative samples are important to provide a better insight into the onset and natural course of depression and AD, as well as regarding our knowledge of the occurrence and influence of depression on cognition in AD in the general population.

The major findings from this thesis may be of both scientific and clinical relevance. With respect to clinical practice, it is important to draw attention to depressive symptoms in the elderly population. Screening for depressive symptoms, both in terms of presence and severity of symptoms, may identify persons at risk for developing both depression and AD, and help preventing depression from becoming a chronic condition among older individuals. Although the available evidence suggests that the constellation of depressive symptoms are different in these two disorders, more research is certainly needed to explore the association of different depressive symptomatologies (i.e., dominance of mood- or motivation-related symptoms) in diseases like depression and AD. Increased insight into early signs may also result in earlier diagnoses and treatment. This is of importance given expected improvements in treatments to slow down the disease progression in AD, as well as the rate of preclinical decline. Besides, the demonstration of elevated depressive symptoms in the preclinical phases of MD and AD should be of relevance with regard to the scientific understanding of the development of these two disorders in very old age.

Another observation of scientific relevance is that we have extended previous findings of negligible effects of depression on cognitive functioning in AD, not only to episodic memory performance, but also to working memory, verbal ability, visuospatial skills, and global cognitive functioning. Thus, there seems to be converging evidence that there is little room for negative effects of depression on cognition in early AD, as opposed to what is true in normal aging. In this regard, depression may act as many other individual difference-variables (e.g., age, sex, education, vitamin $B_{12}$, folic acid, etc) in dementia. However, in the preclinical phase of AD, we reported, for the first time, negative effects of depression on global cognitive functioning. These results may have theoretical implications for understanding the early development of AD. Although depression did not cause accelerated cognitive decline from the preclinical stage to diagnosis, we found cognitive effects of an individual-difference variable (i.e., depressive symptoms) in the preclinical stage of the disease. This finding speaks to the importance of investigating the influence of other subject characteristics on cognitive functioning in preclinical AD. Increased knowledge about the role of various subject-related factors may help identifying individuals at risk for developing dementia.

## DIRECTIONS FOR FUTURE RESEARCH

In this final section, I will outline some avenues for future empirical inquiry derived from the main findings in this doctoral dissertation.

### Psychiatric Symptom Patterns in the Preclinical Phases of Depression and AD

On the basis of the current findings, it would be very interesting to further examine different symptom patterns of depression. First, it is important to replicate our initial findings that mood-related symptoms dominate in preclinical depression, whereas motivation-related symptoms are more common in preclinical AD. Although this pattern may be biologically plausible, it needs to be confirmed in new samples. In addition, it is of interest to expand the focus to other psychiatric symptoms (e.g., anxiety, suspiciousness, social withdrawal) in the onset and course of depression and dementia. For example, suspiciousness and social withdrawal may be more common in prodromal AD as a function of the pronounced cognitive deficits. By contrast, anxiety may be more common in preclinical depression; some evidence suggests that anxiety is a prodrome to depression in elderly people (Loebach Wetherell, Gatz, & Pedersen, 2001). In relation to old age depression, it would also be interesting to learn more about the diffuse somatic symptoms frequently reported by elderly persons as alluded to earlier in the frame, which may be one of the underlying reasons for depression being an underdiagnosed disorder in old age (Gottfries, 2001; Hocking et al., 1995).

Regarding the occurrence of depressive symptoms before the AD diagnosis, it would be a challenge to extend the time frame in detecting preclinical depression-related markers for this disease. Research focusing on preclinical cognitive impairment in AD has documented deficits up to nearly a decade and probably even longer before diagnosis (Bäckman, Small, & Fratiglioni, 2001; Elias et al., 2000). To the extent that cognitively loaded motivation-related symptoms (e.g., lack of interest, concentration difficulties, loss of energy) dominate in preclinical AD, the elevation of such symptoms may follow the same trajectory as specific cognitive measures. Alternatively, measures of episodic memory, executive functioning, and speed may be more sensitive indicators than subjectively assessed motivation-related symptoms many years before diagnosis.

In addition to depressive and psychiatric symptoms in depression and dementia, another interesting area to investigate would be the role of personality traits (e.g., neuroticism) and the association of stress-related factors to the risk for developing depression or AD. Earlier research has indicated that neuroticism may be related to stress-adaptive processes and that the normal aging process affects the stress-regulatory system (Sapolsky, 1990). In addition, past work has documented that high cortisol levels may produce hippocampal damage and cause exacerbated cognitive deficits in old age (Lupien et al., 1999; Lupien & Lepage, 2001). Further, there is preliminary evidence that proness to psychological distress is related to the incidence of AD four years later (Wilson et al., 2003). Thus, an interesting future research line would be to link personality variables and distress proness assessed in young adulthood and midlife to the occurrence of depression and dementia in old age.

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**The Preclinical Phase of Alzheimer's Disease**

An unresolved issue regarding the nature of the preclinical period in AD has to do with the time at which precipitous decline occurs among those who will develop the disease. Although there is consensus that persons who will develop AD show precipitous cognitive decline during the last 2-3 years before diagnosis (Chen, et al., 2001; Rubin et al., 1998; Small, Viitanen, & Bäckman, 1997), evidence is mixed regarding whether accelerated decline is observed longer before diagnosis. In two studies from the Kungsholmen Project, stability of the magnitude of preclinical impairment from 6 to 3 years before diagnosis was observed for measures of episodic memory (Bäckman, Small, & Fratiglioni, 2001) and global cognitive ability (Small et al., 2000). Coupled with other evidence that preclinical impairment may be seen decades before diagnosis (La Rue & Jarvik, 1987; Snowdon et al., 1996; Whalley et al., 2000) pattern suggests that accelerated cognitive decline may not be expected until various biological events (e.g., the accumulation of amyloid and neurofibrillary tangles, inflammation, oxidative stress, loss of synapses, death of neurons) have reached a certain threshold (Hardy & Allsop, 1991; Jobst et al., 1994).

However, other evidence suggests that precipitous decline may occur in persons who will be diagnosed with AD longer before diagnosis. In two studies (Hall, Lipton, Sliwinski, & Stewart, 2000; Hall et al., 2001), accelerated decline in measures of memory was demonstrated more than 5 years before diagnosis. Several factors likely contribute to the equivocal findings, including the nature of the study sample. For example, it is conceivable that accelerated cognitive decline longer before diagnosis is more likely to be observed when strict selection criteria (e.g., removal of persons with other conditions that affect cognitive functioning) are employed. Obviously, more information pertaining this issue is vital in order to achieve a better understanding of the preclinical process in AD, and to improve differentiation between cases and controls.

It may appear self-evident that our knowledge of the trajectory of the preclinical period would be more precise if individuals were to be assessed at many occasions with short follow-up intervals. However, this has to be balanced against the emerging evidence of amazingly strong practice effects in cognitive tasks for older individuals over follow-up periods ranging from 1 (Ferrer, Salthouse, Stewart, & Schwartz, in press) to 5 (Rönnlund, Nyberg, Bäckman, & Nilsson, in press) years.

**Individual-Differences During the Preclinical Period in AD**

An important issue in the preclinical detection of AD cases concerns whether there are individual differences regarding the onset and rate of accelerated cognitive decline. Although individual-difference factors have shown to have limited impact on cognition in clinical dementia (e.g., Bäckman et al., 1999), we found depression-related effects on cognition in the preclinical period of AD. This finding opens up the possibility for potential effects of other health-related factors (i.e., cardiovascular disease, cerebrovascular disease, diabetes, thyroid deficiency, vitamin B deficiency). When considering individual-difference variables in this context, it would also be very interesting to examine interactive effects among different factors with regard to preclinical cognitive performance and decline in AD. Specifically, the issue is whether multiplicative or additive effects would be observed for conditions that, in isolation, may influence the size of the preclinical cognitive deficits in AD (e.g., depression and cerebrovascular disease). Although data

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pertaining to these issues would be valuable to our understanding of early AD development, it is clear that a thorough examination of interactive effects between various health-related factors requires large sample sizes. This is especially true for conditions (e.g., untreated depression) where the occurrence is expected to be relatively low in population-based studies.

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**APPENDIX**

DISSERTATIONS FROM THE DIVISION OF GERIATRIC EPIDEMIOLOGY AND
MEDICINE, DEPARTMENT OF NEUROTEC, KAROLINSKA INSTITUTET, 1998–2004

**1998**

**Bogdanovic Nenad**. Towards a multifaceted approach in neuropathological diagnosis.

**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.

**Fagerberg Ingegerd**. Nursing students' narrated, lived experiences of caring, education and the transition into nursing, focusing on care of the elderly.

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

**Palo-Bengtsson Liisa**. Dancing as a nursing intervention in the care of persons with dementia. (Licentiate thesis).

**Torasdotter Marita**. A Role of neurotrophins in brain plasticity. (Licentiate thesis).

**Hassing Linda Björk**. 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).

**Tham Kerstin**. Unilateral neglect: Aspects of rehabilitation from an occupational therapy perspective.

**Pei Jin-Jing**. Protein phosphatases and kinases implicated in Alzheimer's disease abnormal tau phosphorylation.

**Alyaa Mohammed Ali Mousa**. In vitro studies on human first trimester forebrain cells: Differentiation and interactions with immunoregulating molecules.

**1999**

**Elffors Lars**. Hip fractures – A European perspective.

**von Euler Mia**. Experimental spinal cord injuries – a histopathological, neurogical, and pharmacolo-gical study in the rat.

**Jelic Vesna**. Focus on quantitative EEG in relation to genetic, biochemical and neuroimaging markers.

**Jensen Malene**. Amyloid β-peptide and tau the diagnosis and pathogenesis of Alzheimer's disease.

**Bonkale Willy Lokwa**. Cyclic nucleotide signalling in Alzheimer's disease postmortem brain.

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

**Sonde Lars**. Low-TENS treatment on post-stroke paretic arm. (Licentiate thesis).

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

**Zou Li-Ping**. Immunoregulation and immunotherapy in experimental autoimmune neuritis.

**Axelman Karin**. Clinical, genetic and genealogical investigations of familial Alzheimer's disease. (Licentiate thesis).

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


**2000**

**Eriksson Charlotta**. Region-specific Expression of the Interleukin-1 system in Rat Brain following Endotoxin Challenge and Excitotoxic Neurodegeneration.

**Herzberg Annika**. Relatives' and nursing home staff's experiences of and views on each others. (Licentiate thesis).

**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).

**Jonsson Hans**. Anticipating. experiencing and valuing the process from worker to retiree. A longitudinal study of retirement as an occupational transition.

**Skog Margareta**. Teaching for learning and learning for teaching in care of elderly with dementia at Silviahemmet.

**Andreasen Niels**. Search for reliable diagnostic markers for Alzheimer's Disease.

**Ebbeskog Britt**. Elderly people's daily living with chronic leg ulcer: Evidence and suffering experience. (Licentiate thesis, in collaboration with the Department of Science and Health, University of Karlskrona/Ronneby, Sweden).

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

**Robinson Petra**. Younger persons with suspected and early stage dementia: Their experiences, concerns and need for support. (Licentiate thesis).

**Lilja Margareta**. Elderly disabled persons in the home setting. Aspects of activities in daily life.

**Emami Azita**. "We are deaf, though we hear; we are dumb, though we talk; we are blind, though we see". Understanding Iranian late-in-life immigrants. Perceptions and experiences of health, illness and culturally appropriate care.

**Nilsson Margareta**. Understanding the meaning of past, present and future in advanced age. Very old persons' experiences of ageing.

**Pham Therese**. Effects of neonatal handling and enriched environment of neurotrophins and cognitive function.

**Kumlien Suzanne**. "Nursing care after stroke". (Licentiate thesis).

**Hansebo Görel**. Assessment of patients' needs and resources as a basis in supervision for individualised nursing care in nursing home wards.

**Sunvisson Helena**. Att beskriva och utvärdera betydelsen av interventionsprogram riktade till personer med Parkinson sjukdom för skapande av nya möjligheter att hantera vardagen. (Licentiate thesis).

**Palo-Bengtsson Liisa**. Social dancing as a caregiver intervention in the care of persons with dementia.


**2001**

**Abbas Ahmed Gadeh El Dum Nagat**. Pharmacological and immunological modulation/ manipulation of cytokine and chemokine production in experimental autoimmune neuritis (EAN), a model of inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome). (Licentiate thesis).

**Sennvik Kristina**. A study of the β-secretase cleavage of Alzheimer amyloid precursor protein. (Licentiate thesis).

**Sonde Lars**. Rehabilitation after stroke. Effects of length of stay and treatments to facilitate motor recovery after stroke.

**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.

**Froelich Fabre Susanne**. Genetic studies of frontotemporal dementia.

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

**Ingelson Martin**. Molecular aspects of tau proteins in Alzheimer's disease and frontotemporal dementia.

**Vestling Monika**. Alzheimer's disease mutations and cellular signalling.

## 2002

**Garcia-Jiménez Angela**. G-proteins and adenylyl cyclase in Alzheimer's disease postmortem brain.

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

**Sennvik Kristina**. A study of β-secretase cleaved Alzheimer amyloid precursor protein.

**Cedazo-Minguez Angel**. Apolipoprotein E and Alzheimer's disease: Signals and effects.

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

**Flood Fiona**. Expression studies on the Alzheimer's disease related presenilin and APP genes during development and ageing. (Licentiate thesis).

**Herzberg Annika**. We, not them and us – a utopia? Relatives' and nursing home staffs' views on and experiences with each other.

**Andersen N Christian**. On characterisation and diagnosis of frontotemporal lobar degeneration syndromes. With special reference to the progressive aphasias.

**Hemmingsson Helena**. Student-environment fit for students with physical disabilities.

**Randers Ingrid**. Upholding older adults' innate and inherent dignity within a caring context.

**Nilsberth Camilla**. Distribution and pathophysiological role of amyloid precursor protein and presenilin 1.

**Lindau Maria**. Clinical differentiation between frontotemporal dementia and Alzheimer's disease.

## 2003

**Abbas Ahmed N**. Immunomodulation of cytokine and chemokine production in animal models of neuroinflammatory and neurodegenerative disorders.

**Zhu Yu**. Immunoregulation of experimental autoimmune neuritis focuses on cell immunity.

**Bao Lei**. Immunmodulation and immunopathogenesis in the autoimmune disease with emphasis on autoimmune neuritis and arthritis.

**Ebbeskog Britt**. Elderly patients with slow-healing-leg ulcers.

**Sunvisson Helena**. The embodied experience of living with Parkinson's disease.

**Saletti Anja**. Nutritional status in elderly receiving municipal services and care. (Licentiate thesis)

**Lundberg Catarina**. Older drivers with cognitive impairments: Issues of detection and assessment.

**Mulugeta E**. Muscarinic $M_1$ and $M_4$ receptor subtypes in normal and pathological conditions in the central nervous system: Studies on human and animal tissues using subtype selective ligands.

**Götell Eva**. Singing, background music and music-events in the communications between persons with dementia and their caregivers.

**Huang Chaorui**. Mild cognitive impairment: Neuroimaging markers for early diagnosis of dementia.

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


## 2004

**Bäckberg, Matilda** Hypothalamic neuronal circuits involved in the regulation of food intake and body weight: Histochemical studies in lean rats and obese mutant mice

**Svensson, Dan A** Genetic and environmental influences on major recurrent headaches

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

**Modin, Helena** Multiple sclerosis linkage analysis and DNA variation in a complex trait

**Heikkilä, Kristiina** The role of ethnic identity in care of elderly Finnish immigrants

**Popescu, Bogdan O** Cell death and signal transduction pathways in Alzheimer's disease: The role of presenilin 1

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

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