Psychosocial Factors in Relation to Development of Dementia in Late-life:

a Life Course Approach within the Kungsholmen Project

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To Rebecca, Samuel and Adina

"No man is an island, entire of itself;
every man is a piece of the continent,
a part of the main"

John Donne (1573-1631)

CONTENTS

ABSTRACT - English

This thesis explored social and psychosocial factors from different phases in the lifespan and their relation to the occurrence of dementia and Alzheimer's Disease (AD) in late-life. Early life circumstances, such as education, midlife factors such as occupation, and an active and socially integrated late-life were investigated in relation to dementia and AD risk. All five studies are based on the Kungsholmen Project, a longitudinal population-based study of aging and dementia. The initial population consisted of all registered inhabitants who were 75 years and older and living in the Kungsholmen Parish in 1987. The major findings from the five research papers included in this thesis are summarized below.

Study I. We found that frequent (daily-weekly) engagement in mental, social, or productive activities was inversely related to dementia incidence. Relative risks (RR) and 95% confidence intervals (CI) were 0.54 (95% CI: 0.34-0.87), 0.58 (95% CI: 0.37-0.91), and 0.58 (95% CI: 0.38-0.91), respectively. Similar results were found when these three factors were analyzed together in the same model.

Study II. Less-educated subjects had a RR of 3.4 (95% CI: 2.0-6.0), and subjects with lower socioeconomic status (SES) had a RR of 1.6 (95% CI: 1.0-2.5) of developing AD. Low SES at 20 years of age, even when high at 40 or 60 years, was associated with increased risk. When both education and SES were introduced into the same model, only education remained significantly associated with AD.

Study III. A mental, social, and physical component score was estimated for each leisure activity. RR of dementia for subjects with higher mental, physical, and social component score sums were 0.71 (95% CI: 0.49-1.03), 0.61 (95% CI: 0.42-0.87), and 0.68 (95% CI: 0.47-0.99), respectively. The most beneficial effect was present for subjects with high scores in all or in two of the components.

Study IV. We found that inactivity, depressive symptoms, but not social network, were independently associated with increased risk of dementia. However, to be inactive, have depressive symptoms, and simultaneously have a limited/poor social network compared to having none of these factors showed the strongest association to dementia (RR=5.4, 95% CI: 2.1-13.9).

Study V. Complex work with data and people was associated with reduced risk of dementia (RR = 0.85, 95% CI: 0.75-0.96, RR = 0.88, 95% CI: 0.80-0.97 respectively). When education was included in the model these associations were no longer significant. The association between education and AD/dementia, however, was modified by the highest levels of complexity which had a protective effect even among lower-educated subjects (RR = 0.52, 95% CI: 0.29-0.95).

Summary. The five studies in the thesis identified several sources of cognitive stimulation throughout the lifespan and indicated that education above elementary level, higher levels of work complexity, and a broad spectrum of activities in old age are all related to decreased risk of dementia. The cognitive reserve model can be applied throughout the life course, from childhood to adulthood and late-life, and cognitive ability is modifiable at all stages of life. Conversely, dementia risk is increased by inactivity, loneliness, and low mood; and social isolation intensified the effect of these factors.

Key words: Alzheimer's Disease, dementia, education, socioeconomic status, occupation, leisure activity, social network, depressive symptoms, life course, cognitive reserve, population-based study

ABSTRAKT - Svenska

Denna avhandling behandlar sociala och psykosociala faktorer i olika delar av livet och deras relation till förekomst av demens och Alzheimer's Disease (AD). Skolgång tidigt i livet, yrke i vuxenlivet, och ett aktivt och socialt integrerat liv efter pensioneringen undersöktes i relation till risken att få demens. Samtliga fem studier baseras på Kungsholmsprojektet som är en longitudinell befolkningsstudie om åldrande och demens. Populationen består av boende i Kungsholmens församling som var 75 år eller äldre 1987. De viktigaste resultaten från de fem arbetena i avhandlingen summeras nedan.

Study I. Vi fann att ofta förekommande (varje dag – vecka) mentala, sociala eller produktiva aktiviteter hade samband med minskad demensincidens. Den relativa risken (RR), 95% konfidens-intervall (CI) var 0.54 (95% CI: 0.34-0.87) för mentala, 0.58 (95% CI: 0.37-0.91) för sociala, samt 0.58 (95% CI: 0.38-0.91) för produktiva aktiviteter. Liknande resultat återfanns när alla faktorer analyserades tillsammans i samma statistiska modell.

Study II. Hos personer med låg utbildning var den relativa risken att få AD 3.4 (95% CI: 2.0-6.0) och hos personer med lågt socioekonomiskt status (SES) var risken 1.6 (95% CI: 1.0-2.5). Låg SES vid 20 års ålder, även om man hade hög SES vid 40 eller 60, var kopplat till en förhöjd risk. När både utbildning och SES inkluderades i samma modell, kvarstod endast relationen mellan utbildning och ökad risk för AD.

Study III. För varje fritidsaktivitet skattades en mental, fysisk och social komponent. Samtliga komponenter visade samband med minskad risk för demens: RR=0.71 (95% CI: 0.49-1.03) för den mentala, RR=0.61 (95% CI: 0.42-0.87) för den fysiska, och RR=0.68 (95% CI: 0.47-0.99) för den sociala komponenten. Att ha höga poäng i två eller samtliga komponenter hade gynnsammast effekt.

Study IV. Vi fann att brist på aktivitet och depressiva symptom var oberoende relaterade till ökad risk för demens. Att vara inaktiv, ha depressiva symptom och samtidigt ha ett begränsat eller dåligt socialt nätverk hade den starkaste relationen till demens. (RR=5.4, 95% CI: 2.1-13.9).

Study V. Att ha ett komplext yrke vad gäller data eller människor hade samband med lägre risk för demens (RR = 0.85, 95% CI: 0.75-0.96, respektive RR = 0.88, 95% CI: 0.80-0.97). När utbildning medräknades i modellen var dessa resultat inte längre statistiskt signifikanta. Sambandet mellan utbildning och demens modifierades emellertid av den allra högsta graden av yrkeskomplexitet där vi fann en skyddande effekt även för personer med låg utbildning (RR = 0.52, 95% CI: 0.29-0.95).

Sammanfattning. De fem studierna identifierade ett flertal källor till kognitiv stimulans under livsloppet och visade att både hög utbildning, högre grad av komplexitet i yrkeslivet samt ett brett spektrum av aktiviteter i senare delen av livet kunde minska risken för demens. Hypotesen om en "kognitiv reserv" kan användas som förklaringsmodell från den första ända till senare delen av livet, och den kognitiva förmågan är möjlig att påverka under alla stadier av livet. Risken för demens ökar vid förekomst av inaktivitet, ensamhet och nedstämdhet och social isolering skärper ytterligare effekten av dessa faktorer.

Nyckelord: Alzheimers sjukdom, demens, utbildning, socioekonomiskt status, yrke, fritidsaktiviteter, socialt nätverk, depressiva symptom, livslopp, kognitiv reserv, befolkningsstudie.

LIST OF ORIGINAL PAPERS

This doctoral thesis is based on the following original papers, which are referred to in the text by their Roman numerals.

I. Wang HX, **Karp A,** Winblad B, Fratiglioni L.

Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen Project. *American Journal of Epidemiology* 2002;155:1081-7.

II. **Karp A**, Kareholt I, Qiu C, Bellander T, Winblad B, Fratiglioni L.

Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease. *American Journal of Epidemiology* 2004;159:175-83.

III. Karp A, Paillard-Borg S, Wang HX, Silverstein M, Winblad B, Fratiglioni L.

Mental, physical, and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and Geriatric Cognitive Disorders. (Accepted)*

IV. Karp A, Parker MG, Berger AK, Wang HX, Winblad B, Fratiglioni L. The contribution of depressive symptoms, inactivity and social isolation to the development of dementia in the elderly. A 6 year follow-up from the Kungsholmen Project. (*Submitted manuscript*)

V. Karp A, Andel R, Parker MG, Winblad B, Fratiglioni L. Work complexity and the risk of dementia and Alzheimer's Disease – a follow up study. *(Manuscript)*

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ApoE ε4 allele	Apolipoprotein E ε4 Genotype
CES–D	Center for Epidemiological Studies–Depression survey
CI	Confidence Interval
CPRS	Comprehensive Psychopathological Rating Scale
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third-Edition Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Forth Edition
HSCL	Hopkins Symptom Checklist
HSFR	Swedish Council for Research in the Humanities and Social Sciences
ICD-8	International Classification of Diseases, Eighth Revision
MMSE	Mini-Mental State Examination
NIH	National Institutes of Health
NYK	Nordisk Yrkesklassificering. Nordic Version of the International Standard Classification of Occupations
OR	Odds Ratio
RR	Relative Risk
SBU	Swedish Council on Health Care Assessment
SEI	Socioekonomisk Indelning. Swedish Socioeconomic Classification.
SEM	Structural Equation Measurement Models
SES	Socioeconomic Status
SNACK	Swedish National Study of Aging and Care in Kungsholmen
VaD	Vascular Dementia

INTRODUCTION

Dementia, the individual and society

One common reply from an elderly person to the question "How are you" is the following: "As long as my mind is still working I really don't want to complain". Although good dementia care is available today, and in spite of the fact that no healthy person really knows the actual pain and joy of the demented elderly, the loss of one's independence through this disease appears to be one of the most dreaded conditions of old age. Dementia is a major cause of disability [1] and mortality [2] among the elderly. Around 5% of the population aged 65 years and older is affected by dementia [3] and the prevalence rises exponentially, with the rate nearly doubling every 5 years between 65 and 85 years of age [4]. Among the oldest old (90-95 years) dementia prevalence is 30%-40% [5] and in the most advanced ages (95+) as high as 45% [4]. Detecting factors that can prevent or postpone the disease is of great value from a societal, family and individual point of view. Interventions that could delay disease onset even modestly would have a major positive public health impact [6], and the prospect of dementia prevention may also reduce some of the common fears and anxieties of becoming older.

Definition of dementia and Alzheimer's disease (AD)

Dementia is a clinical syndrome that is characterized by progressive loss of cognitive capabilities serious enough to interfere with normal daily functioning including social and professional functioning [7]. Multiple cognitive domains deteriorate, including memory impairment together with at least one other cognitive disturbances such as aphasia, apraxia, agnosia, or disturbances in executive functioning. Alzheimer's Disease (AD) is the most common subtype of dementia accounting for approximately 50-70% of all prevalent dementia cases. AD diagnosis requires an insidious onset, a gradual and progressive deteriorating course, and the exclusion of all other specific causes of dementia [7,8]. AD is classified as a neurodegenerative disease as opposed to dementia of vascular origin (VaD), which accounts for 20-30% [4]. The diagnosis of VaD requires abrupt onset, stepwise deterioration, history of stroke, and/or focal deficits [9]. Lately however, researchers have started to recognize a considerable overlap between the two dementia types, especially among the oldest old. Despite important progress in the medical treatment of dementia and AD there is currently no cure for these disorders. Conversely, most lifestyle factors are modifiable and the detection of the effect of the risk due to such factors may lead to the identification of important preventive strategies.

Epidemiology of dementia and Alzheimer's disease

Epidemiology is the study of how disease is distributed in a population and the factors that influence or determine this distribution [10]. Knowledge and understanding of dementia and cognitive decline has grown dramatically over the last two decades. At the moment, researchers agree that dementing disorders are multi-factorial, and are caused by an interaction of genetic and environmental factors acting during the whole life of the individual [4]. According to consistent results from several studies risk factors for dementia and AD are: old age, apolipoprotein E ε4 genotype (ApoE ε4 allele), familial aggregation, and mid-life hypertension [4,11,12]. Mid-life lifestyle factors such as body mass index [13,14], or elevated cholesterol levels (> 6.5 nmol/L) [15] have recently been suggested as risk factors for dementia and AD. An active and socially integrated lifestyle in late-life, including mental and physical activities and social network, are currently receiving increasing attention as protective factors [16].

Social and psychosocial factors during the life course

Although the title of this thesis only mentions psychosocial factors, it deals in fact with both social and psychosocial factors which are investigated separately or combined in relation to dementia and AD risk. In a recent report the National Institutes of Health (NIH) stated that: "…*social* factors are important contributors to health and illness and frequently interact with biological factors to influence health outcomes. They also represent critical avenues for treatment and prevention. The term "social" encompasses sociocultural, socioeconomic, and sociodemographic status; to biosocial interactions; and to the various levels of social context from small groups to complex cultural systems and societal influences [17]."According to Hemingway and Marmot, 1999, a psychosocial factor can be defined as "a measurement that potentially relates *psychological* phenomena to the social environment and to pathophysiological changes…..Psychosocial factors may act alone or combine in clusters and may exert effects at different stages of the life course [18]."

When studying diseases and conditions in old age it is logical to consider the influence of factors operating also at other stages of the individual's life. Even events that occurred more than 70 years back in time might be of great importance for diseases in old age such as dementia. Life course epidemiology – defined as the study of long-term effects of physical or social exposures during gestation, childhood, adolescent, young and old adulthood, on later health and disease risk - has been increasingly influential during the last decade. A number of different models have been developed [19,20]. One model emphasises the possibility of

critical periods for certain risk factors which will influence the health later in life [21]. An alternative model suggests that a *cumulative lifetime exposure* of physical and social environments may increase the risk of later diseases. Another view is to regard the risk factors as clustering together in a temporal sequence to form *a chain of events* that ultimately increases risk of disease [22,23]. These models may of course operate simultaneously and it is sometimes difficult to separate them empirically [19].

Finally, sociohistorical influences act throughout an individual's life course. It is likely that such factors were active in the present study population as well. For example, seven years of education was standard regardless of a child's intelligence at the beginning of the twentieth century. Above this mandatory educational level essentially children of more privileged groups could ascend, whereas in Sweden today even children with severe mental disabilities are guarantied ten years of schooling [24]. Another example is the typical upward social mobility that was fairly common in Sweden after the Second World War. Moreover, socio-cultural patterns and structures of leisure activities after retirement [25] and family structures are continuously changing.

The life course approach may be challenging since a person's lifetime from birth (or even conception) to old age theoretically encounters an almost infinite number of influencing factors, some of them detrimental and some of them beneficial. They all interplay with each other in a way that the available data bases and the current methodologies have difficulties in fully capturing. In spite of this, studying factors from different periods of the lifespan of the elderly is essential in order to go beyond one-dimensional views of what influences diseases in old age. Finally as a model, the life course approach provides a structure for a more complete data collection to of the most crucial events in a lifespan, as well as for an continuing discussion on all major events that may have been missed.

The social and psychosocial factors addressed in this thesis are: education, occupation-based socioeconomic status (SES), occupational complexity, post-retirement leisure activities, social network and depressive symptoms in old age. Education refers to schooling during the first two decades of life, socioeconomic status and work complexity refers to the young and middle age working life, and leisure activities and social network concerns the ages 75 years or older. Using the data derived from the Kungsholmen Project´s database, we have investigated these factors, hypothetically interrelated as in the model reported in Figure 1.
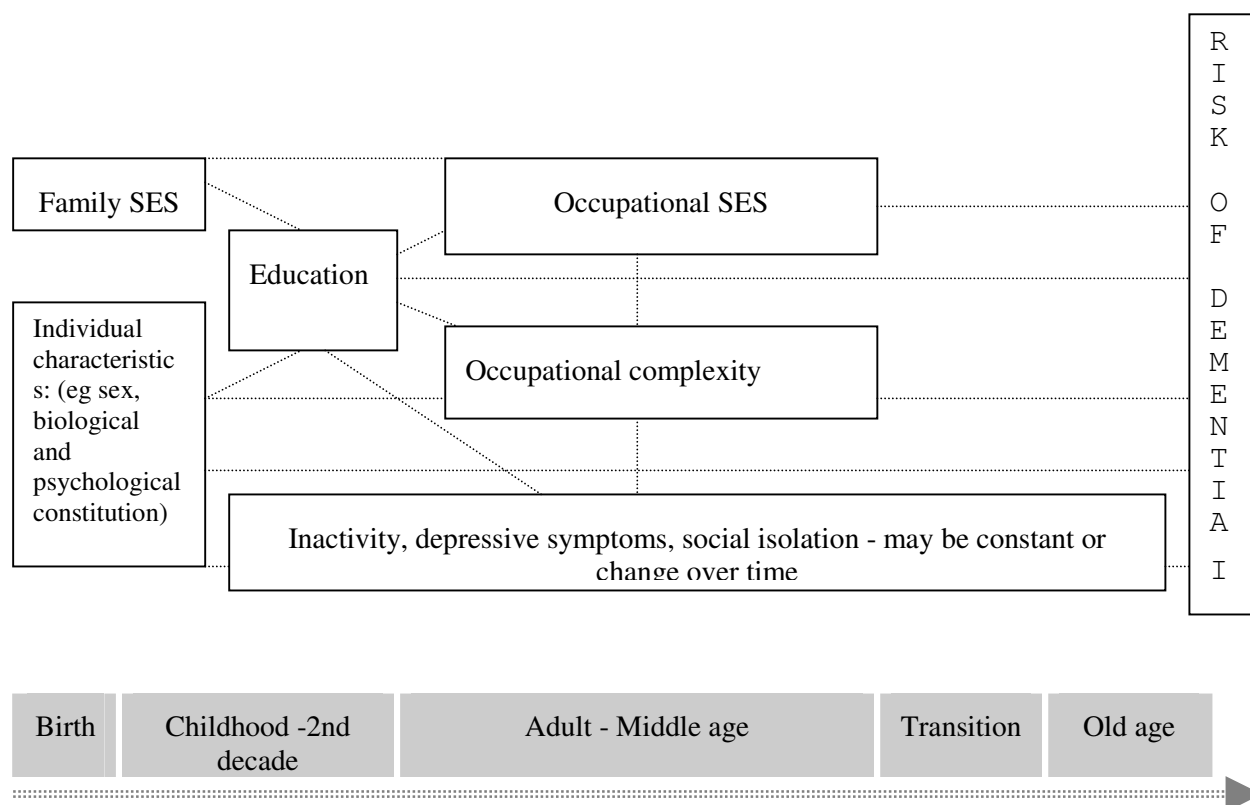
Figure 1. Hypothetical model of the timeline of psychosocial factors in relation to each other and dementia risk

Education

Many incidence studies have reported an increased risk of dementia and AD in lower educated subjects [26-32]. Fewer have failed to detect any relation [33]. Education may play different roles, maybe more than one at a time, in the etiopathogenesis of dementia and AD. Education is a marker of cognitive abilities which may have both environmental and genetic influences [34]. Education is also a provider of cognitive stimulation and an indicator of early social and economic factors which may be of importance for dementia risk in old age.

Education as cognitive stimulation

One of the main suggestions regarding which mechanisms could be accountable for the association between education and dementia was offered by Katzman, 1993, who proposed that education might enhance the brain reserve by increasing synaptic density in the neocortical association cortex [27]. Stern et al, 1994, who suggested a cognitive reserve, expanded the reserve hypothesis by taking into account the possible beneficial influence of mental activity throughout the entire life-span, where occupational attainment along with level of education could influence the risk of AD [28]. High education protects against the functional consequences of the neuropathology and hence delays the disease rather than

protect against acquisition of the disease [35]. In the hypothetical model shown below, the cognitive development for two imaginary patients, one with high and one with low education is visualized as different levels of cognition. Time when AD pathology begins, as well as the slope of the neurodegenerative process are assumed to be the same for both individuals. The cognitive reserve is depicted as the two different spans or areas of resources to cope with the pathology.
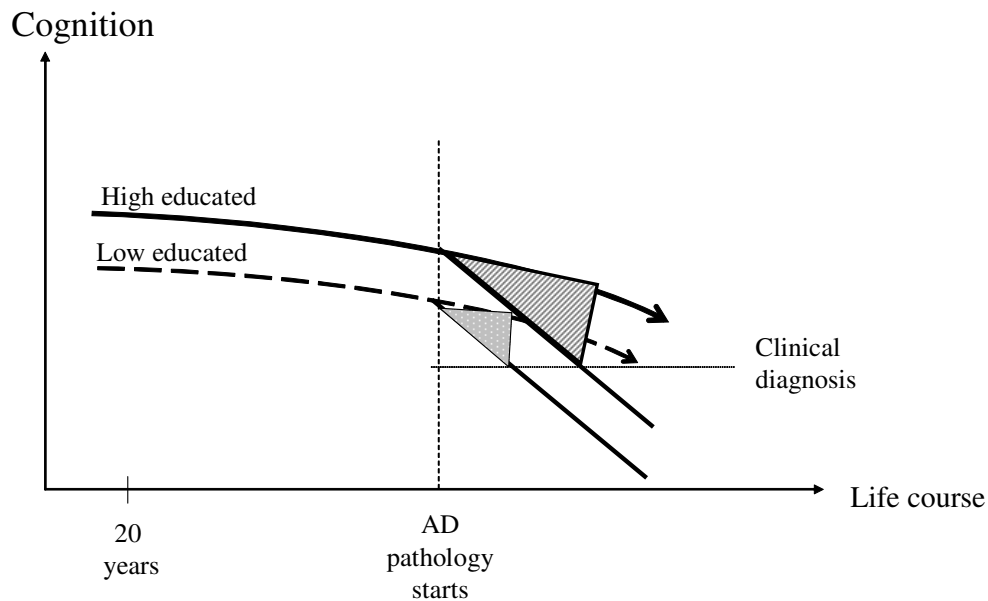

Figure 2. Hypothetical model of cognitive reserve due to education

Education an indicator of circumstances in early life

Education is one of the markers of SES which may be defined as: "A composite measure that typically incorporates economic status, measured by income; social status measured by education; and work status measured by occupation" [36]. While occupational status may change during the lifetime, education is, in most cases, acquired in childhood and young adulthood and hence it may represent a proxy for socio-economic or environmental influences in childhood [37]. Indeed, "education is a good indicator of the social backgrounds of the children as well as of their level of knowledge and skills" [38].

A study of education and dementia within a middle to high socio-economic Italian population proposed that the first decade of life could be a critical period for developing dementia later in life [39]. Poor-quality childhood or adolescent environments have been suggested to prevent the brain from reaching complete levels of maturation, which in turn may put people at higher

risk of dementia and AD [40]. The same study group [41] further suggested that ApoE ε4 allele may modify the associations between father's occupation, other early-life environmental factors, and development of AD in late-life. Most studies concerning early life factors have used cross-sectional design and prevalent cases except the Religious Orders Study. This study with a ten-year long follow-up did not support the hypothesis that early life SES is related to risk of AD [42].

Occupation

Occupation is one of the most important features of adult life. Outside of being a principal prerequisite of income, forming personal growth and identity, as well as a criterion for social stratification, occupational settings produce the most pervasive and continuous demands during life [43]. Several aspects of working life have been of interest as possible risk factors for dementia and AD. Since there is such large number of different types of occupations, a major problem is to classify them in a way that catches underlying factors of relevance for the development of dementia and AD. Schulte et al, 1996 [44] explored whether there were specific occupational clusters for neurodegenerative diseases (including AD) and reported occupations involving pesticides, solvents, electromagnetic fields, and also legal, social, and religious work. Furthermore, occupation type such as "realistic occupations", including trade, technical and service occupations, have been reported as predictor of poorer cognitive performance and a higher prevalence of DSM-III-R dementia [45]. Occupation has further been explored as a source or indicator of SES [46], work stress [47], adverse exposures [48], demands [49], and complexity [50] in different domains. The present thesis will focus on two main characteristics of occupation: 1) SES and 2) occupational complexity.

Occupation-based SES

While education level stresses differences between people in terms of access to information and the proficiency to benefit from new knowledge, and income stresses differences in access to material goods, occupational status includes both these aspects and additionally the benefits accrued from the exercise of specific jobs, such as prestige, privileges and power [51]. Differences in morbidity and mortality between socioeconomic groups have been observed in many studies and constitute one of the most consistent findings in epidemiologic research [52]. The main hypotheses aiming at explaining these findings are briefly summarized in the Table1.

Table 1. Three hypotheses concerning the relation between SES and health

<u>Neomaterial intepretation</u>: Even in times and places where the most basic material conditions are satisfied, each step up the income ladder may bring added neomaterial benefits that can produce gains in health. The neomaterial interpretation further states that health inequalities result from the differential accumulation of exposures and experiences that have their sources in the material world [53].
<u>Health behaviours</u>: eg. smoking, physical activity, alcohol consumption are often linked to SES. The association between SES and morbidity or mortality may be explained by the higher prevalence of health risk behaviours among those with lower SES levels [54,55]. SES differences in health have been found to be reduced but not eliminated when these factors are taken into account [56].
<u>Psychosocial and stress-related factors</u>: Low control, insecurity, and loss of self esteem are among the psychosocial risk factors known to mediate between health and SES [57]. The likelihood of encountering negative events such as work stress and having fewer social resources to cope is increased in lower SES groups [58]. Recently, SES related psychosocial stress has been suggested to decrease health through a reduction of cardiac parasympathetic regulation [59].

Rather few studies have reported an association between adult SES based on occupation and the incidence of AD or dementia. Evans et al, 1997 [30] found that all investigated markers of SES (education, occupational prestige and income) predicted the development of AD.

Manual work, when it involves goods production, may increase the risk of clinical AD or dementia, particularly among the younger old [60]. In a population-based study from Finland low income level at old age was found to be related to dementia, but not low income level at midlife [61]. In a case control study with autopsy-confirmed AD, educational attainment and SES of AD patients were not significantly different than in subjects who died in hospital from other diseases [33].

Occupational complexity

Kohn and Schooler, 1978 [62-64] found that non-demented older workers who had an intellectually demanding and complex occupation better maintained their cognitive function. Schooler proposed a hypothesis of environmental complexity, which suggests that highly complex environments offering many opportunities for participating in self-directed and

substantively complex tasks increase intellectual flexibility, thereby promoting a relatively stable cognitive functioning in older adulthood [63,64]. Furthermore complexity of work with data, people, and things was investigated in relation to AD in a sample from the Swedish Twin Registry [50]. The study found that each additional level of complexity of work with people was associated with a 22% reduction in AD risk in case-control analyses, and that both complexity of work with data and people were protective in co-twin control analyses. This is in line with the cognitive reserve hypothesis [28,65] (Figure 2) which emphasises the role of mental stimulation throughout the entire life-span.

Leisure activities

Leisure activities may be defined as the non-lucrative activities that individuals perform for their own pleasure. After retirement, leisure activities usually constitute a relatively larger part of daily life than before, and may take on the role of providing mental stimulation, social engagement and physical activity that was provided by school or employment in young and middle age. Furthermore, engagement in activities has been suggested as adaptive strategy to compensate for social and physical deficits in old age [66]. Participation in leisure activities and maintaining a good social network have been reported to be associated with lower risk of dementia and AD [67-76]. In an extensive review article the authors[16] concluded that there is currently sufficient support that an active and socially integrated lifestyle in late-life can decrease the risk of dementia. Engagement in leisure activities has been hypothesized to produce more efficient cognitive networks, thereby providing a cognitive reserve that could delay the onset of the clinical manifestations of dementia [77,78]. This hypothesis has been supported by the findings that mentally stimulating activities, in particular, may be linked to reduced risk of dementia and AD [71-73].

The hypothetical model in Figure 3 shows the cognitive development for two imaginary patients with the same level of education but different activity levels in adult life. Time when AD pathology begins is assumed to be the same for both individuals as well as the slopes of neurodegeneration. The triangular areas describe the cognitive reserve as the resources to cope with the pathology and illustrate the dissimilarity between the active and less active person.
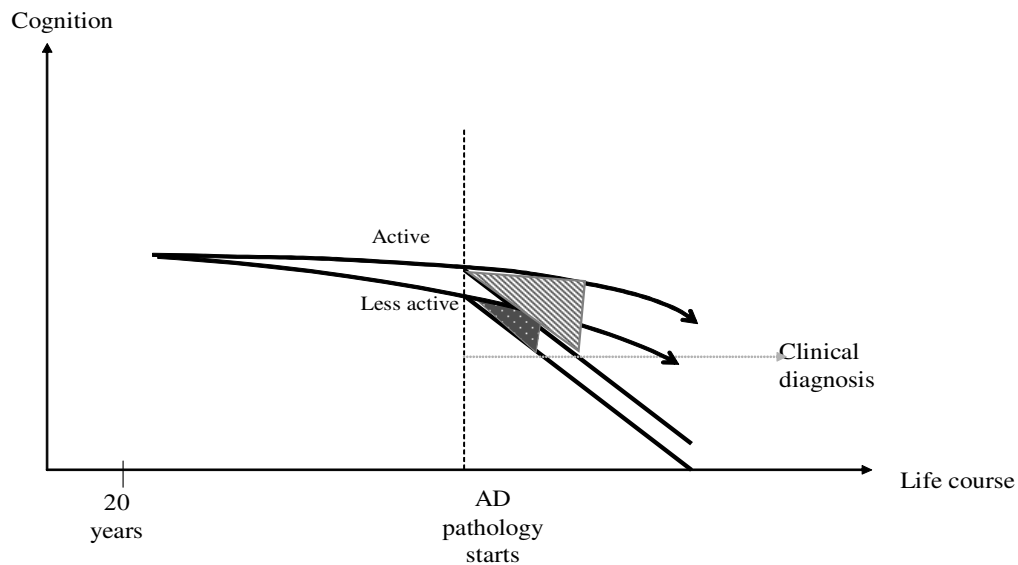
Figure 3. Hypothetical model of cognitive reserve due to activity

Regular physical activity was suggested as protective and as an important component of a preventive strategy against AD [79,80] and dementia [81] and, in women, against cognitive decline at six to eight years of follow-up [82] However, other studies did not confirm such an association [75].

Social network

Social network can be defined as the web of social relations that surround the individual and the characteristics of those ties [83]. Social environment is important for the psychological balance and has been suggested to protect against depression among elderly persons [84,85]. When resources, such as social network support, are scarce, older individuals seem to be more vulnerable to aging losses [86]. A rich social network has been found to exert a protective effect against dementia [69,87].

Loneliness and low mood

Elderly who live without a partner generally report more social and emotional loneliness [88] Feeling lonely is an emotional reaction to loss of friends and marriage partner or general lack of companionship, but it may also be a symptom of depression. Loneliness and low mood are two questions commonly asked about when measuring depressive symptomatology in the elderly, such as in the Center for Epidemiological Studies–Depression survey (CES–D) [89] and the Hopkins Symptom Checklist (HSCL) [90]. Some studies have proposed that depression may be a risk factor for dementia [91,92]. Findings from the Religious Order

Study [93] suggested that the association of depressive symptoms is approximately linear and that risk is increased even in person with predominantly mild symptoms. For each depressive symptom, risk of developing AD increased by an average of 19%, and there is also an increased risk of AD in persons with mild depressive symptoms. However, it is also possible that depressive symptoms may be early manifestations rather than predictors of AD or dementia [94,95].

Current evidence linking psychosocial factors with dementia

An extensive and systematic review of the literature starting from 1986/01/01 concerning risk and protective factors for dementia and AD was prepared by Fratiglioni et al, 2005 [96] for the dementia-risk factors-group at the Swedish Council on Health Care Assessment (SBU).

A final quality index for each study was calculated by following a four-step procedure where 1) the internal validity was quantified taking into account population type, drop-out rate, case ascertainment, diagnostic procedure, exposure assessment, confounding control, presence of bias, and statistical power; 2) three specific causal criteria were examined for each article and their quality graded: strength of the association, temporality and biological gradient; 3) the single items for both aspects (internal validity and causal criteria) were summarized in a score including four categories: not acceptable, insufficient, acceptable, and appropriate; 4) the two aspects were integrated in a final quality index: not acceptable, low, medium, and high (Table 2).

Table 2. Final quality index from the SBU 2005, calculated by a four-step procedure

Final quality index			
Quality / Quantity	**Low**	**Medium**	**High**
Insufficient	Insufficient	Limited	
Limited			Moderate
Moderate			
Substantial			Strong

The evidence from the literature for each specific putative risk/protective factor was summarized by taking into account both quality and quantity of the reports (Table 3).

To be regarded as a risk factor, a minimum follow-up time of six years was required for leisure activities and depression.

Table 3. Number of accepted studies from the SBU 2005 - Risk factors working group

	Association	No Association	Evidence
Low education	10	2	Moderate
Low SES	3	2	Insufficient
Work complexity	2	0	Insufficient
Leisure activities	14	2	Moderate
Social network	3	1	Insufficient
Depression	7	1	Insufficient

Among the above factors only education and leisure activities were considered to have moderate evidence of an association to dementia and AD. More research is needed regarding the other putative risk or protective factors.

AIMS

This thesis explores the following hypothesis: Early-life circumstances, such as education may create a long-term reserve that is still important in old age, midlife factors such as occupation may also generate a reserve capacity, and a stimulating active late-life may in addition support the functional plasticity of the aging brain. Specific aims are:

1) To explore the relation between social and leisure activities in late-life and the development of dementia (**Study I**);

2) To verify whether the reported association between low education and increased risk of AD and dementia could be explained by occupation-based SES (**Study II**);

3) To detect which specific component (mental, physical, and social) could explain the reported protective effect of leisure activities; and to compare the role of the major components in dementia risk (**Study III**);

4) To investigate the combined effect of inactivity, depressive symptoms, and social isolation on dementia development (**Study IV**);

5) To evaluate the association between work complexity factors and dementia risk, and to verify whether the association between education and dementia may be modified by occupational complexity (**Study V**).

METHODS

The Kungsholmen Project

All five studies are based on data from the Kungsholmen Project, a longitudinal population-based study of aging and dementia. The initial population consisted of all registered inhabitants who were 75 years and older and living in the Kungsholmen Parish in 1987 (n=2368). Of these eligible subjects, 181 individuals had died, 69 had moved out of the area, and 308 refused to participate at the baseline examination.

Baseline survey (1987-1989) [97,98]. A total of 1810 persons (76.4%) participated in the initial survey, in which demographic, cognitive, social network, and leisure activity data were collected. A Swedish version of the Mini-Mental State Examination (MMSE) [99] was used as a screening test for possible dementia (Phase I). At the first clinical examination, 314 subjects with suspected dementia (MMSE<24) and a sample of subjects without cognitive impairment (n=354) underwent an extensive medical examination. This was the clinical phase of the baseline survey (Phase II). Dementia diagnoses were made according to the revised diagnostic criteria in the third version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) [7]. Of the 1810 participants who underwent the baseline examination, 1473 were diagnosed as non-demented. All participants were re-examined using the same extensive protocol at each follow-up, each with approximately three-year intervals. At the time of the first follow-up, an additional data collection concerning occupational history was carried out. Specially trained nurses interviewed a relative or another person significant to the subject, about the full lifetime work history.

Follow-up examinations [100]. Four waves of follow-up examinations have been completed, each with an average interval of three years. At every follow-up occasion the surviving subjects underwent structured interviews by nurses, clinical examinations by physicians, and neuropsychological assessments by psychologists. If the subject was not able to answer, an informant, usually a next-of-kin was interviewed. For those subjects who had died before the follow-up examination, information regarding their health status was obtained from the Stockholm Computerized Inpatient Register System which is a register of discharge diagnoses from all hospitals in Stockholm since 1969. The individual hospital records, discharge diagnoses, as well as the death certificates were examined.

Study population

Data used in this thesis were derived from the baseline survey (1987-1989), the first follow-up (1991-1993), and the second follow-up (1994-1996) of the examinations of the Kungsholmen population.

Studies I, III, and **IV**. Of the 1473 subjects diagnosed as non-demented at the clinical phase of the baseline survey (Phase II), 98 subjects whose MMSE scores were less than, or equal to, 23 or who were living in an institution were excluded from the present study because institutionalisation or impaired cognition may limit the person's activity. By the first follow-up examination, 269 subjects had died, 172 refused participation, and 934 participated. Of these, 158 were diagnosed as demented and were excluded from the analysis. Thus, the population for these studies was composed of those 776 persons participating and still non-demented at the first follow-up examination. As 44 subjects refused to participate to the second follow-up, 732 subjects were followed for another three years (second follow-up) to detect incident dementia.

Study II The cohort of 1473 non-demented subjects were investigated to detect incident dementia. In addition to the 172 persons who refused to participate or had moved, information about lifetime occupational history was unavailable for 370 subjects due to refusal by informants. The current study therefore consisted of 931 persons.

Study V. Similar to Study II, the study population consisted of 931 persons. Among the 626 subjects who were alive and remained free of dementia at the first follow-up, 500 subjects underwent the second follow-up examination (1994-1996) and one person refused participation.

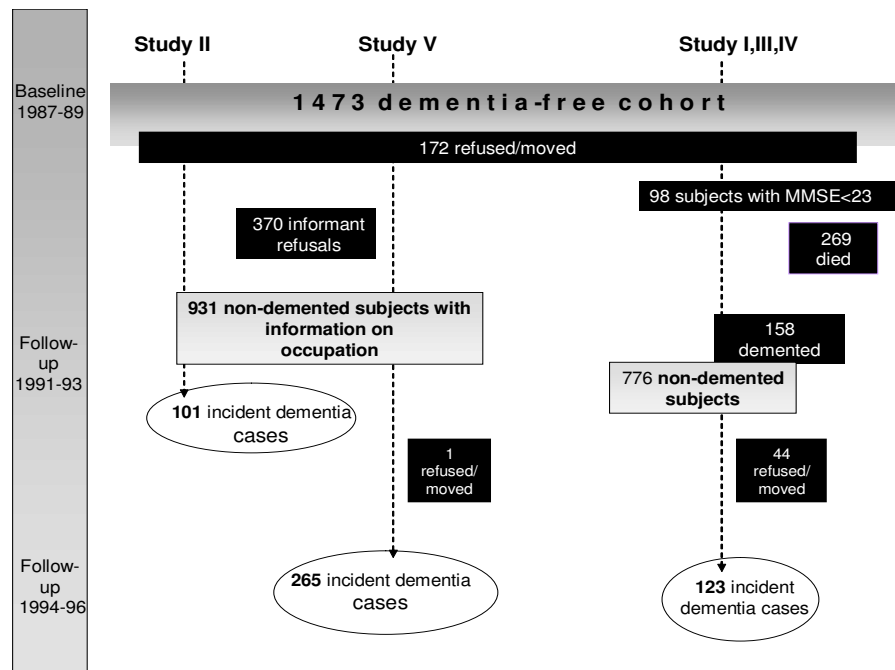These five study populations are illustrated in Figure 4.

Figure 4. Study populations of studies I-V

Dementia diagnoses

At baseline, prevalent dementia cases were identified through a two-phase design [97]. At each follow-up, all surviving participants were assessed with a clinical examination by physicians and by psychologists. A family interview was carried out by nurses. The incident dementia cases were all individuals who developed dementia during the follow-up period. The diagnosis of clinical dementia was made according to DSM III-R criteria [7] using a three-step procedure. First, a preliminary diagnosis was made by the examining physician. Second, all cases were independently reviewed by a specialized clinician and a second diagnosis was made. If those diagnoses were in agreement this was the final decision. In case of disagreement, a third opinion was asked for and the concordant diagnosis was accepted. The diagnoses were labelled as "clinically definite dementia", when DSM-III-R criteria was completely fulfilled and "questionable dementia" when there was evident memory impairment but dysfunction of a second cognitive ability was questionable. The diagnosis of AD required gradual onset and progressive deterioration of dementia, and that all other specific causes of dementia had been excluded.

For the deceased subjects, a preliminary diagnosis was made by a physician through consulting medical records and finally reviewed by a senior clinician. When only discharge diagnoses from hospitals or from death certificates were available, the reported diagnosis was accepted. The time of the dementia onset was assumed to be the midpoint between the date of the screening test at baseline and date of the follow-up examination or death.

Assessment of independent variables

Education

Information about total years of formal schooling was collected at baseline. Persons with an intermediate education (8-10 years of schooling) did not differ in AD risk from university-educated subjects (11+ years of schooling). Based on previous analyses [32], educational level was divided into two main categories: 2-7 years (six years of elementary and in some cases one extra year of practical vocational training), and ≥ 8 years (intermediate and university). Data on educational background were missing for three persons, and these subjects were omitted from all the analyses concerning education.

Occupation

At first follow-up, specially trained nurses interviewed a relative or another significant person about the full lifetime work history of each subject. The use of informants was due to the fact that some subjects were already cognitively impaired at the time of the first follow-up, and to reduce potential informant bias all information about occupation was collected through informants. The interview questionnaire was developed by an expert in occupational medicine and explored lifetime work activities concerning employer, job title, time period, and tasks for all jobs lasting at least six months. The longest job of the subject was defined as the main occupation. Quite a few women (21%) were homemakers for the longest occupational period. Depending on which aspect of occupation was investigated, the grouping of the housewives varied (see below).

SES. All occupational periods were grouped according to the Swedish socioeconomic classification system (SEI) developed by Statistics Sweden [101]. The classification system primarily contains dimensions of ownership of means of production, and the division into blue-collar and white-collar occupations assessed by normal trade-union affiliations. It also contains aspects of skills in the subdivisions inside blue-collar and white-collar occupations. The SEI classification consists of 18 basic SEI-categories.

In its most aggregated form the classification system consists of six groups (Table 4):

Table 4. Socioeconomic classification used by Statistics Sweden

SES Group	Definition	SEI code
1	Unskilled and semiskilled workers	11-12
2	Skilled workers	21-22
3	Assistant non-manual employees	33-36
4	Intermediate non-manual employees	44-54
5	Employed and self-employed professionals, higher civil servants and executives	54-60
6	Self-employed (other than professionals)	76-87

In case of the subjects being housewives in the longest period, their second longest occupation was used for estimating SES. Data concerning their husband's occupation, which is a frequently used estimation of the SES of wives, was not available. Eighteen subjects had been housewives all their working lives and were excluded in the analyses concerning SES.

Subjects who were farmers in the longest job (n=2) were included in the self-employed category.

Occupational complexity. First, the main occupation was grouped according to the Nordic version of the International Standard Classification of Occupations (NYK) in the way it was used in the Swedish census in 1980. Subjects who had been housewives in the longest period were classified as being engaged in "other housekeeping and related work". In a previous study [50], each occupational category from the 1980 Swedish census was matched to the best-fitting category in the 1970 US Census [102]. Two independent raters, one based in the United States and the other in Sweden, performed the code matching. A disagreement of ten percent of the matching was found, and these cases were discussed until the two raters reached a consensus. Next, occupational complexity scores, from a matrix developed by Roos and Treiman [103], were applied for each occupational category. The scores reflect those from the Fourth Edition of the Dictionary of Occupational Titles [104] where more than 12,000 occupations were rated from on-site observations by qualified job analysts across the US [105]. Each occupational title was rated according to its level of complexity with data, people, and things. The score system for each work category included in the three major groups is reported in Table 5.

Table 5. Characteristics and scores for complexity of work with data, people, and things

Complexity of work with <u>data</u>		Score
	Synthesizing	*6*
	Coordinating	*5*
	Analyzing	*4*
	Compiling	*3*
	Computing	*2*
	Copying	*1*
	Comparing	*0*
Complexity of work with <u>people</u>		**Score**
	Mentoring	*8*
	Negotiating	*7*
	Instructing	*6*
	Supervising	*5*
	Diverting	*4*
	Persuading	*3*
	Speaking-signalling	*2*
	Serving	*1*
	Taking instructions-helping	*0*
Complexity of work with <u>things</u>		**Score**
	Setting up	*7*
	Precision working	*6*
	Operating-controlling	*5*
	Driving-operating	*4*
	Manipulating	*3*
	Tending	*2*
	Feeding-offbearing	*1*
	Handling	*0*

Detailed information of the characteristics of work performed at each level of complexity is presented in Appendix A.

Leisure activities

Information on leisure activities was obtained from the subjects by means of a personal interview carried out by trained nurses at baseline. Subjects were asked whether they regularly engaged in any particular activities, the type of activities, and the frequency of participation. The reported leisure activities were grouped into 29 main types of activities. The reported activities were treated in two ways:

1) The activities were categorized according to whether they were predominantly mental, physical, social, productive, or recreational (**Study 1**). See Table 6 below.

Table 6. Classification of leisure activities (Study I)

Mental activity	Reading, writing, studying, doing crosswords, painting, or drawing
Physical activity	Swimming, walking, or doing exercise
Social activity	Theatre, concerts, art exhibitions, travelling, playing cards/games, social group, or pension organizations
Productive activity	Gardening, housekeeping, cooking, working after retirement, doing volunteer work, or handicraft
Recreational activity	Watching television or listening to the radio

2) A mental, social, and physical component score was assigned to each of the 29 activities (**Study III**). Two raters independently assigned scores to each activity based on their own evaluations and then discussed with a third rater in order to reach a consensus. The grading of the three components was coded as: 0=none, 1=low, 2=moderate, 3=high. To validate the scoring, 13 cognitively intact, elderly raters (seven men, six women), 75 years or more, but not participants in the Kungsholmen Project, were asked to individually fill in a small questionnaire containing a list of all 29 activities together with scoring instructions.

Depressive symptoms at baseline

At baseline, a psychiatric evaluation was conducted on a smaller sample, rather than the whole population. However, two single depressive symptoms were assessed at baseline by a structured nurses' interview concerning health problems. The subjects were asked the following questions: "Do you often feel in a low mood?" and "Do you often feel lonely?" A new, combined dichotomized variable was created, in which having none of these symptoms was coded as 0 and having one or two symptoms was coded as 1. At first follow-up, depression was diagnosed using the DSM-IV [106] criteria for major depressive disorder. The majority of the person reporting any or both of the two depressive symptoms did not develop major depression three years later, although it was more common to develop depression in this group compared to the group of elderly who did not report any symptoms at baseline (Table 7).

Table 7. Cross-tabulation between depressive symptoms at baseline and depression diagnosis at first follow-up

		Depression diagnosis at first follow-up (1991-1993)	
		No	Yes
Depressive symptoms	No	515 (97.7%)	12 (2.3%)
at baseline (1987-1989)	Yes	174 (87.0%)	26 (13.0%)

Social network

Data on social network was obtained from the subjects through a personal interview carried out by trained nurses at baseline. The structure of social network included four elements: marital status, living arrangement, parenthood, and friendship. Marital status was recorded as being married, single, divorced, or widowed. Living arrangements included living alone or living with a spouse, a partner, children, or siblings. Parenthood was measured by asking whether the subject had children and in such case what was the frequency of their contact. Friendship was assessed by asking whether the subject had close friends or relatives and the frequency of contact. The quality of the network resources was measured by the degree of satisfaction with the available contacts.

Both structure and perceived adequacy of the social network were then integrated into a single index that consisted of the following four categories: extensive, moderate, limited, and poor social network [69]. *Extensive social network* included subjects who had all of the following components: a) being married and living with someone, b) having children with daily to weekly satisfying contact and c) having friends/relatives with daily to weekly satisfying contact. *Moderate social network* included persons who had any two of the three components, and *Limited social network* included persons who had any two of the components, and *Poor social network* included persons who had none of the three components. Due to the small number of subjects in the *Poor* social network category, the four-grade social network index was dichotomized for the analyses in **Study IV**. *Poor* and *Limited* social network were merged into one category, and *Moderate* and *Rich* social network were merged together for a second category.

Assessment of the covariates

Age and gender collected at baseline were considered as basic potential confounders in all five studies. In **Studies I, III**, and **IV** education, cognitive function, depressive symptoms, physical function, and comorbidity were considered as potential confounders. Cognitive function was measured with the

MMSE [99]. Physical function was defined as disability in at least one of the basic activities of daily living (ADL): bathing, dressing, toileting, continence, feeding, or transfer [107]. Data concerning diseases occurring before baseline were obtained by reviewing hospital discharge diagnoses through the Stockholm Computerized Inpatient Register System. These diseases were diagnosed according to the International Classification of Disease, 8th edition (ICD.8; WHO, 1967): coronary heart disease (ICD-8: 410-414), cerebrovascular disease (ICD-8: 430-438), diabetes mellitus (ICD-8: 250), malignancy (ICD-8: 140-208 and 230-239), and hip fracture (ICD-8: 820). Comorbidity was defined as one or more of these five diseases.

In **Study II** and **Study V**, vascular diseases, and data on alcohol consumption were added to the basic covariates age and gender. Vascular diseases included coronary heart disease, cerebrovascular disease, and diabetes mellitus assessed as reported above. Also included were heart failure (ICD-8: 428), arrhythmia (ICD-8: 427), and arterial blood pressure measured at baseline with a mercury sphygmomanometer. A simple additive index was created including the vascular diseases or risk factors described above.

Information about alcohol use was collected from relatives specifying how many glasses of wine, bottles of beer, and/or glasses of liquor the subject consumed weekly. Due to low alcohol consumption in this elderly cohort (82.4% of the persons reported that they did not consume any alcohol), alcohol data was divided into three categories: no use, any use, and no information. The latter category was included in the analyses since reporting alcohol is a sensitive matter, and thus it was relevant to consider whether absence of information per se was associated with the risk of dementia.

In **Study IV** we additionally controlled for depression diagnosed at first follow-up using the DSM-IV criteria [106] for major depressive disorder. A physician expert in geriatrics and psychiatry made the diagnoses based on the results from the psychiatric examination and interview using the Comprehensive Psychopathological Rating Scale (CPRS) [108].

Statistical analyses

Table 8 summarizes the outcome variables, the determinants under study, and the potential confounders that were considered in the five studies. Specific analyses for each study are also reported.

Table 8. Statistical models used in the different studies (Studies I-V)

Study	Statistical model	Outcome	Factors	Covariates	Regression models*
Study I	Cox proportional hazards models	Dementia	Leisure activities	Age, sex, education, MMSE, comorbidity, depressive symptoms, ADL	In a first model, engagement in each type of activity was analyzed by examining participation vs no participation. Second, engagement in each type of activity was introduced as a five-grade indicator variable with no participation as reference. Finally a reduced three-grade indicator variable for each activity type was derived and entered either one by one or simultaneously into the same model.
Study II	Cox proportional hazards models	Dementia, Alzheimer's Disease	Education, Occupation-based SES, Socioeconomic mobility	Age, sex, vascular disease index, alcohol consumption	The first set of models explored education or occupation, and education and occupational SES included in the same model. The second set of models investigated the interrelation between education and SES by combining: high education and high SES; high education and low SES; low education and high SES; low education and low SES. Furthermore, by combining low and high education as defined above, with permanence in low SES for less than or equal to/more than 25 years. Third, a model exploring social mobility patterns consisting of combinations of low or high SES at 20, 40, and 60 years was carried out.
Study III	Cox proportional hazards models	Dementia	Leisure activities (mental, physical, social components)	Age, sex, education, MMSE, comorbidity, depressive symptoms, ADL	The first set of analyses were performed for each of the mental, physical, and social leisure components, contrasting subjects with one, and two or more moderately/highly scored activities with subjects without any moderately/highly scored activity. Second, the sum of scores for each person and each component were analyzed using a) the continuous variable b) four groups with similar number of cases, and c) two groups dichotomized according to the median value.
Study IV	Cox proportional hazards models	Dementia	Leisure activities, Social network, Depressive symptoms	Age, sex, education, MMSE, comorbidity, depression at first follow-up; ADL	The first models included each of the following variables: lack of activities, limited/poor social network, and depressive symptoms. The second set of models combined participation in activities and depressive symptoms into a four-category indicator variable, and analyzed this variable in relation to risk of dementia. The third set of models stratified for social network. Finally, the combined effect of the three variables (activity, depression, and social network) were analyzed by using an eight-category indicator variable and furthermore reduced into a four-grade indicator variable. Additionally, we controlled for the presence of major depression diagnosed three years (first follow-up) after the baseline examination.
Study V	Cox proportional hazards models	Dementia, Alzheimer's Disease	Occupational complexity with data, people, and things	Age, sex, education, vascular disease index	In the first models, the continuous complexity scales concerning work with data, people, and things were analyzed one by one. Secondly, education was included in the models. Each of the complexity dimensions were then divided into approximate medians and quartiles and analyzed separately as well as including education in the regression models. Furthermore, alternate dichotomizations dividing at higher levels of the dimensions were analyzed as above. All analyses were repeated with stratifications for education. Finally, the combined effect of work complexity and education was analyzed by using four category variables.

*All models were first carried out with adjustments for age and sex, and then including the other covariates.

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ETHICAL CONSIDERATIONS

All eligible persons living in the Kungsholmen district were contacted personally with a individualized letter explaining the content, duration, and purpose of the study, as well as the importance of participation, but clearly stating that it was voluntary and that at any time they could discontinue participation. They were then directly contacted via telephone by a nurse in order to check their availability and to book the first visit. For all participants, informed consent was requested directly at the screening evaluation. The aims of the project were explained and confidentiality of the information provided by the subjects or informants was stressed. If the person was severely cognitively impaired, a proxy was asked for consent (usually a close family member). It was agreed, as a general rule, that the examination or interview should be interrupted if the person in any way expressed anguish or discomfort, regardless of whether informed consent had been given directly by the person or by a proxy.

In addition, all phases of the Kungsholmen Project received approval from the Ethics Committee at the Karolinska Institutet of Stockholm, Sweden.

All five studies in thesis included data collected from the baseline survey to the second follow-up evaluation. It further included data from medical records, death certificates, and the inpatient register database. For each phase, approval from the Ethics Committee at the Karolinska Institutet was obtained:

Baseline survey (Phase I and II):   Dnr. 87:148;

First follow-up (Phase III):   Dnr. 90:251;

Second follow-up (Phase IV):   Dnr. 94:122

Death certificates and the Stockholm Inpatient Register data: Dnr. 99:025; Dnr 01:020.

In addition, all researchers working with the Kungsholmen Project database follow the guidelines of the Swedish Council for Research in the Humanities and Social Sciences (HSFR) [109]; the principles of autonomy and integrity, the rule of consent, and the demand for research.

RESULTS

Results in a life course perspective

The results from **Studies I-V** will be presented according to where in the lifespan they were most likely to have had an effect.

Relations between the psychosocial variables

The investigated psychosocial factors are significantly inter-correlated when investigated in a bivariate fashion (see Figure 5). Educational and occupational factors are positively correlated to each other and negatively correlated to the psychosocial factors. For correlations between the psychosocial factors see **Study IV**.
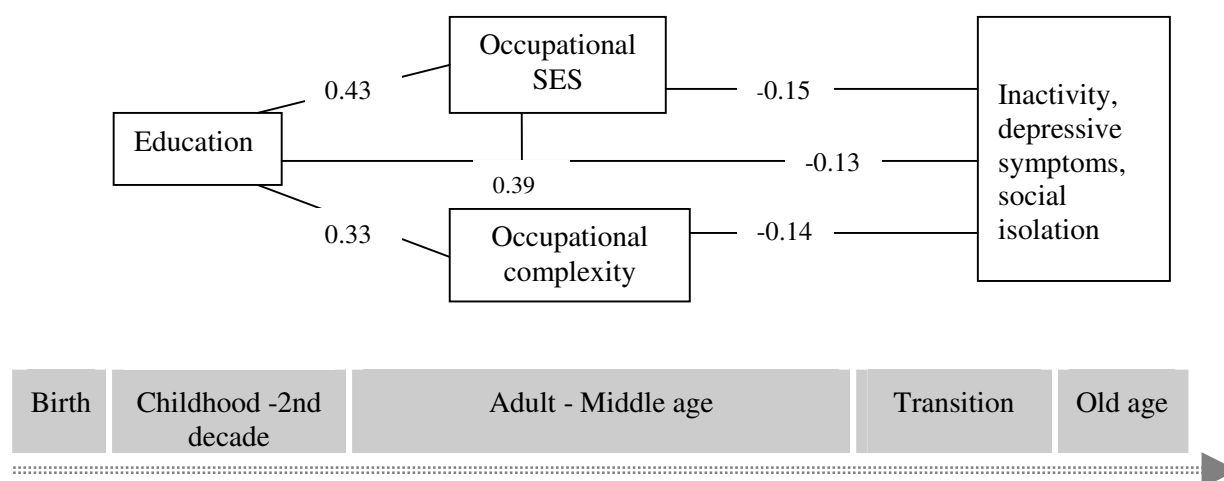
Figure 5. Bivariate correlations (Spearman's Rho) between social and psychosocial factors in a hypothetical lifespan perspective (All correlation coefficients are significant (p<0.05)

Education and work at 20 years of age may be regarded as indicators of early life conditions in the first two decades of life. **Study II** showed that low education was associated with increased AD incidence. Less-educated subjects had a RR for AD of 3.4 (95% CI: 2.0-6.0) after adjusting for age, gender, vascular diseases, and alcohol use. This association was not mediated by low adult occupation-based SES. Furthermore, having low occupation-based SES at the age of 20 was significantly associated with AD (RR=1.9, 95% CI: 1.2-3.0) when controlling for age, gender, vascular diseases, and alcohol use.

Adult - Middle age

Adult life psychosocial factors were represented by occupational SES and complexity. **Study II** showed that subjects with low SES had a RR of 1.6 (95% CI: 1.0-2.5) of developing AD after adjusting for age, gender, vascular diseases, and alcohol use. Subjects with low SES at 40 or 60 years of age had only borderline significantly increased risks. When education was introduced in the models, occupation-based SES was no longer significantly related to dementia and AD, and this was regardless of whether SES was measured as the subject's longest occupation, SES at 40 or 60 years of age, or assessed as ≥ 25 years in a low SES position.

When education and occupation-based SES were investigated in combination we found that low education in combination with either low or high occupation-based SES was associated with an increased risk for dementia and AD, even after adjustment for the major covariates. The combination of high education and low occupation-based SES was not associated with any increased risk of dementia or AD (Figures 6a and 6b).
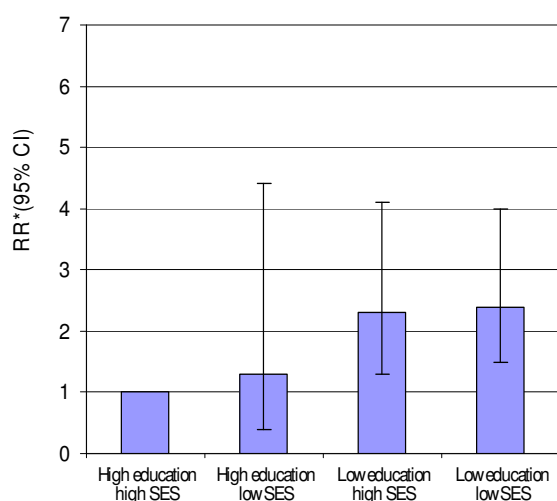

Figure 6a. Relative risks* (95% CI) of dementia in relation to combinations of SES and education
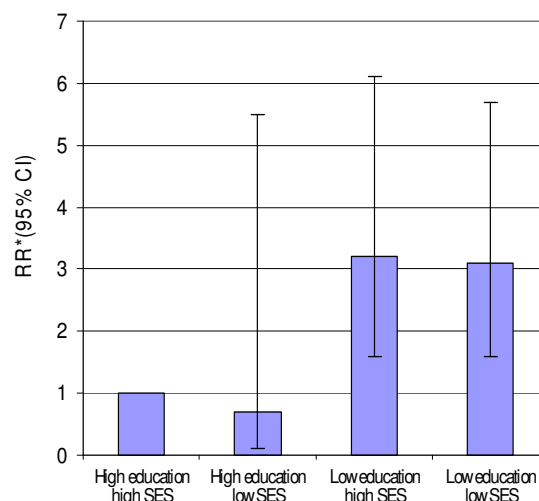

Figure 6b. Relative risks* (95% CI) of AD in relation to combinations of SES and education

*adjusted for age, sex, vascular diseases index, and alcohol data.

Results from **Study V** show that complexity of work with data and with people was associated with reduced risk of dementia (RR= 0.85; 95% CI: 0.75-0.96, RR= 0.88; 95% CI: 0.80-0.97 respectively) and AD (RR = 0.85; 95% CI: 0.77-0.95, RR= 0.86; 95% CI: 0.77-0.96) when controlling for age and gender. When education was included in the model these associations were no longer significant. The association between education and dementia/AD was however modified by the highest degrees of complexity (analyzing, coordinating or synthesising data). In these levels of complexity of work with data reduced risk of dementia and AD was found even among lower educated subjects (Figures 7a and 7b).
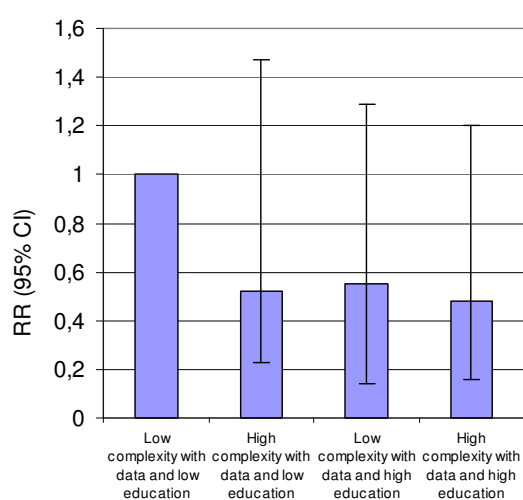

Figure 7a. Relative risks* (95% CI) of dementia in relation to combinations of work complexity and education

Figure 7b. Relative risks* (95% CI) of AD in relation to combinations of work complexity and education

*adjusted for age, sex, and vascular diseases index.

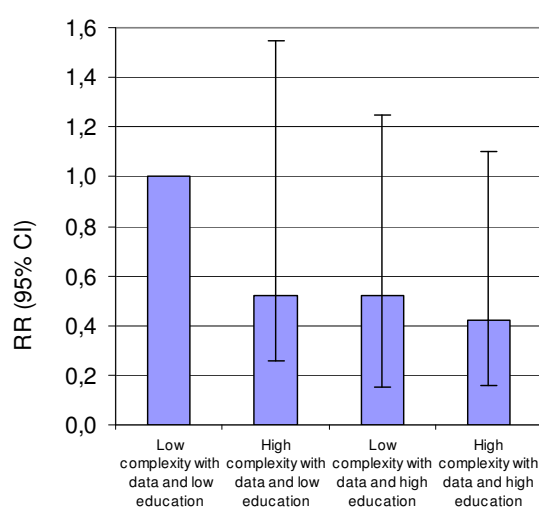_Transition_   _Old age_

In **Study I, Study III**, and **Study IV** social and psychosocial conditions in old age were investigated in relation to dementia risk. After adjustment for age, gender, education, cognitive functioning, comorbidity, depressive symptoms, and physical functioning at the first examination, frequent (daily-weekly) engagement in predominantly mental (RR = 0.54, 95% CI: 0.34-0.87), social (RR = 0.58, 95% CI: 0.37-0.91), or productive (RR = 0.58, 95% CI: 0.38-0.91) activities was inversely related to dementia incidence. In **Study I**, similar results were found when these three factors were analyzed together in the same model (Figure 8).
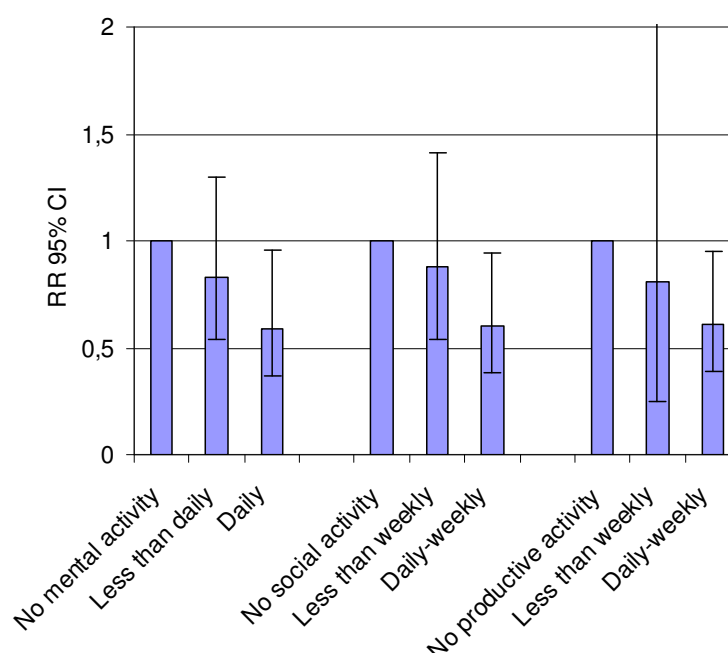
Figure 8. Relative risks* (95% CI) of dementia in relation to type of activities from the same model

*adjusted for age, sex, education, baseline MMSE, comorbitity, physical functioning, and depressive symptoms.

In Study III, a mental, social, and physical component score was estimated for each leisure activity. Each of the components was associated with lower risk of dementia (Table 9). The mental component score sum, when categorized in four grades, showed a significant trend (p=.043) in relation to dementia risk. There was no trend with regard to the four score sum categories for the physical or social components.

Table 9. Relative risks* (95% CI) of dementia associated with higher vs lower mental, physical, and social leisure score sums

	No. of subjects	No. of cases	RR (95% CI)*
Higher mental score	372	48	0.71 (0.49-1.03)
Higher physical score	447	56	0.61 (0.42-0.87)
Higher social score	368	48	0.68 (0.47-0.99)

*adjusted for age, sex, education, baseline MMSE, comorbitity, physical functioning, and depressive symptoms.

The mental, physical, and social components were further merged into an index with four categories: 1) low score in all three components, 2) high score in one component, 3) high score in two components, or 4) high score in all three components. Having high scores in two or three of the components was associated with a significant reduction in risk of dementia (Figure 9).
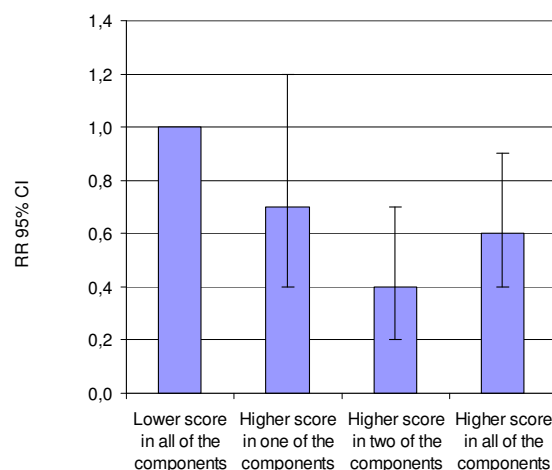
Figure 9. Relative risks* (95% CI) of dementia associated with combinations of higher or lower mental, physical, and social score sums

*adjusted for age, sex, education, baseline MMSE, comorbitity, physical functioning, and depressive symptoms.

When those having higher scores on two or more of the components were combined (category three and four together), the relative risk ratio fell to almost half (RR = 0.53, 95% CI: 0.36-0.78). The most beneficial effect was present for subjects with high scores in all or in two of the components (RR of dementia = 0.53, 95% CI: 0.36-0.78).

In **Study IV**, lack of activities, depressive symptoms, and social isolation in old age was investigated. Inactivity, depressive symptoms, but not social network, were independently associated with increased risk of dementia when adjusting for age, gender, education, cognition, comorbidity, and physical functioning. When we stratified for rich-moderate and poor/limited social network there was a combined effect of inactivity and depressive symptoms, with a RR of 5.47 (95 % CI: 1.56-19.11) inside the limited-poor network stratum. Having one, two, or three of the factors showed a dose response relation to dementia incidence (Figure 10).
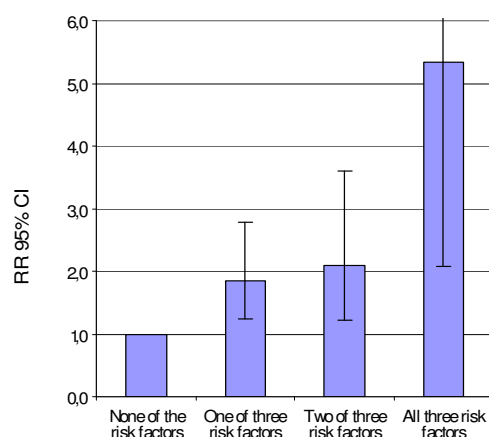

Figure 10. Relative risks* (95% CI) of dementia in relation to inactivity, depressive symptoms and limited/poor social network

*adjusted for age, sex, education, baseline MMSE, comorbidity, and physical functioning.

DISCUSSION

In this thesis, psychosocial factors were investigated in relation to the risk of dementia and AD using three and six year follow-up data in a community sample of elderly who were 75 – 101 years at baseline. The main findings are summarized in the following points:

- Low education was associated with an increased risk of dementia and AD and was not mediated by adult occupation-based SES or socioeconomic mobility.

- Low occupation-based SES was associated with increased risk of dementia and AD, but was no longer significantly associated with dementia and AD risk when education was included in the model.

- Occupational complexity of work with data and people was associated with a decreased risk of dementia and AD, but the effects were partly explained by education.

- The association between education and dementia/AD was modified by the highest degrees of complexity (analyzing, coordinating, and synthesizing data) which was associated with a decreased risk even among lower-educated subjects.

- Frequent engagement (daily-weekly) in mental, social, and productive activities decreased the risk of dementia. Similar results were found when these factors were analyzed together in the same model.

- Engagement in leisure activities with mental, social, and physical content in late-life was associated with a decreased risk of dementia, and a broad spectrum of activities appears to be more beneficial than being engaged in only one type of activity.

- Inactivity, depressive symptoms, but not social network, were independently associated with an increased risk of dementia.

- Inactivity, depressive symptoms, and social isolation, taken together, substantially increased the risk of dementia in old age, and social isolation modified the effect of the two other factors.

The discussion will cover potential methodological issues, compare the findings with previous research, and analyze possible interpretations of the results.

Internal validity

Selection bias

In the Kungsholmen Project, a dementia-free cohort was identified by a two-phase design at baseline through a screening phase for all participants and a clinical phase for those who screened positive and a sample of those who screened negative [97,98]. In the screening phase some very mild dementia cases, in particularly those with high education, may have been missed and consequently been classified as non-demented. Moreover, diseases, such as dementia, with a long preclinical phase, may result in differential selection of exposed and non-exposed according to disease status (before it is clinically apparent) [110].

Another source of potential selection bias is the drop-outs. Among the 2368 elderly inhabitants of the Kungsholmen parish who were invited to participate, a total of 558 persons (23.6%) never took part due to death (32%), refusal (52%), or moving from the area (15%). In comparison with those who participated in the screening phase, the drop-outs due to death were older and more often men. The people who refused or moved did not differ from the participants with regard to age and gender. The social and psychosocial situation of the non-participants was not known to us but hypothetically there may have been a systematic bias if persons with low SES in a prodromal phase of dementia were less likely to participate. This may have lead to an underestimation of the association between low SES and risk of dementia.

Individuals lost to follow-up tend to have different probabilities of the outcome than those who remained in the cohort [110]. Among the persons who agreed to participate, 110 more persons dropped out in the clinical phase of the baseline survey. Of the 1473 non-demented subjects identified at baseline, 172 (11.7%) were lost to follow-up due to refusal or moving out of the area. The drop outs did not differ with respect to baseline demographic features except that more persons in the oldest category (90+) and people more affected by vascular disease dropped out [111]. Among those who remained free of dementia at the first follow-up, as few as 44 persons (5.6%) refused the second follow-up. Due to this low dropout rate it is less likely that this bias may have affected **Studies I, III**, and **IV**.

In **Study II** and **Study V**, 370 informants refused to participate in the occupational interview. The missing subjects were comparable to the participants in terms of age, gender, and vascular disease, but differed in level of education. Since low education was related to AD

and dementia this may have affected our results, but most likely towards an underestimation than an overestimation of the relation between education and dementia.

Misclassification of disease

All dementia and AD diagnoses were clinically-based because neuroimaging was not feasible in a large scale population-based study like the Kungsholmen Project. This may have affected the diagnostic accuracy, but the diagnostic procedure was made through consensus among three independent physicians and has been validated with relatively high overall agreement (κ=0.70) on diagnosis [112]. Although misclassification of disease may have occurred, it is likely that it was non-differential.

There may, however, have been a "diagnostic bias" due to education in such a way that the lowest educated subjects may have been diagnosed at an earlier point in their disease processes. This could have affected the results, particularly in **Study II**, which reported an association between low education and elevated risk of dementia and AD.

Misclassification of exposure

As with the disease diagnosis, the exposure may be biased by misclassification.

In **Study I** and **Study III,** open-ended questions were used to obtain information concerning engagement in leisure activities. Open questions can be of great value because they capture a wide variety of possible and sometimes unexpected answers [113], but there is always a risk of a systematic difference in how people report activities, which may be related to the outcome or some important confounder. In **Study III** we repeated the analyses excluding the subjects who did not report any activities at all (as well as treating them as a separate group), and the results were largely similar. Furthermore, in **Study IV**, no validated inventories were used to assess social network and depressive symptoms. Only two depressive symptoms were measured and although they are included in the CES-D Scale [89], they could not capture depressive symptomatology with the same reliability of the full scale.

In **Study II** and **Study V,** the occupational data was obtained through informants. However, a single open-ended question about occupation had already been asked to the participants at baseline, and when these responses were compared there was an 80 percent agreement concerning SES. The Swedish system for classification of SES from occupation in **Study II** is a well-established and evaluated [114] scheme, but interpretation is always necessary when occupational is coded into different SES categories. The estimation of SES from occupation was particularly difficult for the subjects who were housewives in the longest period (21%). It is likely that our

approximations resulted in non-differential misclassification of SES, leading to a dilution of its association to dementia and AD, particularly when the more precisely estimated variable education was included in the same model.

In **Study V** we estimated work complexity from occupational data that were first classified according to the Swedish census occupational categories and then linked to the US Census occupational categories and complexity ratings from the "Dictionary of Occupational Titles". The inter-rater agreements in the above matching procedures were high [50] but nevertheless there may be some imprecision due to cross-cultural differences.

Potential confounding

Major confounders which are potentially associated with both outcome and determinant variables were assessed. Their effects were controlled for by performing stratified analyses and addressed simultaneously by multivariate regression. However, since lifestyle and psychosocial variables are interrelated the question could arise as to which covariates may be intermediary in the causal pathway between exposure and disease. In **Study II**, for example, we reported all risk estimates in two models: 1) adjusted only for age and gender, and 2) additionally adjusted for alcohol consumption and cardiovascular diseases. In this case the results did not differ. The issues concerning confounding have been further discussed in each of the studies.

Interpretations of the findings and external validity

Low education was associated with increased risk of dementia and AD and was not mediated by adult occupation-based SES.

Our results are in agreement with previous findings of a positive association between low education and increased risk of AD and dementia [26-32]. This is in line with the hypothesis that education may create a reserve [27,28,115]. Our findings may also support the more debated suggestion that the deleterious effects of low education may be due to early-life SES or poor-quality childhood or adolescence [40-42]. Furthermore, the proposal that lower education is mainly indicative of lower intelligence that is the real predictor [116] of dementia can not be disregarded from our results, since we lack data concerning premorbid intelligence.

Low occupation-based SES was associated with increased risk of dementia and AD, but was no longer significant when education was included in the model.

Only a few studies have simultaneously investigated these two markers in relation to risk of dementia or AD. Evans et al [30] reported that each of the socioeconomic measures predicted AD risk, but when they were included in the same model, only education but not income and occupational prestige retained a significant association with AD. A study from Italy found that education but not occupation (blue collar, white collar, farmer, or housewife) was associated with AD and vascular dementia [117]. Analogous findings of a strong association between low education and cognitive decline, but little association with other markers of SES have been reported from the Nurses' Health Study [118]. To definitely conclude that occupation-based SES is significantly less important than education in terms of causal relationships may be premature, since these two variables are correlated and education is likely to be the more precisely measured variable of the two.

Occupational complexity of work with data and people was associated with a decreased risk of dementia and AD, but the effects were largely explained by education.

We found a significantly decreased risk of dementia and AD associated with complexity of work with data and people when the complexity scores were analyzed continuously, controlling for age and gender. When we also adjusted for education there were similar tendencies, although they were no longer statistically significant.

Overall, our findings concerning complexity of work are consistent with the results of Andel et al, 2005 [50] who found that greater complexity of work was associated with reduced AD risk when controlling for age, gender, and education. Their case-control analyses found complex work with people was associated with reduced AD risk whereas in their co-twin control analyses the same pattern was found for complex work with data. No other study, to our knowledge, has investigated work complexity with data and people in relation to dementia and AD risk. A major strength of our study is that it is community-based with relatively long follow-up and specifically designed to evaluate relations between occupations and dementia/AD.

Highest levels of complexity of work with data, showed a significant association with decreased risk of dementia even among participants with a low level of education.

Within occupations involving complex work with data, we found that the categories *"analyzing", "synthesising"* and *"coordinating"* were associated with a decreased risk of dementia as opposed to *"compiling data" and "lower categories"* (See Appendix A). In the dimension concerning occupational complexity with people, there was no specific category

significantly related to a lower risk of dementia, although there was a tendency for a potential threshold between "*Persuading*" and higher complexity vs "*Speaking-Signalling*" and lower complexity.

Our study supplements earlier results by indicating that there may be a work complexity threshold in relation to dementia risk, at which "presenting alternative actions" at work rather than "carrying out prescribed actions" may be necessary to decrease dementia risk among people with low levels of education. This is in line with the assumption that rich opportunities for participating in self-directed and substantially complex tasks may increase intellectual flexibility and promote stable cognitive functioning in old age [63]. Additionally, not only does it support the hypothesis of a cognitive reserve, but also that the cognitive reserve can be enriched even at the adult stage of the life course [28].

Frequent engagement in mental, social, and productive activities decreased the risk of dementia.

These findings confirmed the beneficial effect of an active life on dementia that had been proposed by others [67,68,119,]. Our study overcame some of the methodological limitations of the earlier studies. Data about activities were collected several years before dementia diagnosis, and important confounders such as comorbidity, depressive symptoms, as well as cognitive and physical function were considered. Later studies with longer follow-up times further verified our results [70,71,73,76]. Some studies have also found that physical activity may preserve cognitive function and decrease the risk of dementia and AD [68,70,79,80], which we did not see in **Study I**.

A broad spectrum of activities is the most beneficial.

Our study confirmed earlier results stating that engagement in leisure activities with mental, social, and physical content in late-life is associated with decreased risk of dementia [16]. Although other researchers [120,73] have acknowledged the fact that most leisure activities consist of several overlapping components, nobody to our knowledge, has attempted to separate the different components from each other. We found that even small contributions of the mental, physical, or social components of common leisure activities mattered when they were accumulated. As few elderly people engaged in vigorous exercise, the benefit of light physical components in activities that are not primarily physical, is especially noteworthy.

Inactivity and depressive symptoms of loneliness and low mood were independently associated with increased dementia risk.

The study verifies the importance of activity in old age in relation to dementia [16] and supports earlier suggestions [91-93] regarding depressive symptoms as a possible risk factor for dementia. Our study differed from others since we assessed depressive symptoms with simply two questions concerning loneliness and low mood, yet found a strong association between these symptoms and increased risk of dementia. To have limited/poor social network was not significantly associated with incident dementia in this six-year follow-up study. In an earlier study [69] from the Kungsholmen Project with a three-year follow-up there was a significantly increased risk of dementia for subjects with limited/poor social network. The difference in results between the two studies could be due to the exclusion of all incident dementia cases identified at first follow-up in the present study. In addition, our study population was older, and more time had passed since the baseline assessment of social network.

Social isolation modified the effect of inactivity and depressive symptoms.

When inactivity, depressive symptoms, and social isolation were combined into an index, we found a considerably higher risk of dementia for individuals who had all three factors compared to having none of the factors. A case-control study [87] earlier investigated psychosocial factors as a combination between social ties and activities, and found an associated risk of dementia and AD. When we further stratified for social network index, the combination of inactivity and depressive symptoms was associated with a five times higher risk of dementia compared to being active and having no depressive symptoms, within the stratum of limited/poor social network. It is possible that a good social network may buffer some of the otherwise more adverse effect of depressive symptoms and lack of activities [121]. Since all three independent variables were assessed at baseline, it was not possible to establish any temporal order of their occurrence.

Are the psychosocial factors causally linked to dementia?

To what extent could the psychosocial factors play a causal role in the development of dementia and AD? Some of the psychosocial factors share common hypothetical interpretations such as the idea of a reversed causality. Depressive symptoms, inactivity, and isolation may be preclinical symptoms rather than risk factors of dementia. Education, SES, and complexity at work may be confounded by premorbid intelligence. The brain reserve [27]

hypothesis, as well as the cognitive reserve [28] hypothesis, primarily propose *protection against the functional consequences* of neuropathology [35]. Other hypotheses such as the vascular and the stress hypotheses suggest mechanisms that may *explain* the associations. Psychosocial factors could act through effects of vascular disorders or risk factors that may be involved in the pathogenesis and progression of dementia and AD [16]. Psychosocial factors may buffer against stress, and failure to cope with stress may play a part in the pathogenesis of dementia [122,123]. Dementing disorders are caused by an interaction of genetic and environmental factors, and according to these hypotheses psychosocial factors may be causal components in the development of the disease. Churchill et al, 2002 [124] suggested that the brain may respond to physical exercise with neurogenesis, at least in the hippocampus, and learning and mental activity enhances the survival of neurons. Furthermore, Cabeza et al, 2002 [125] found that age-related neural decline could be counteracted among high-performing older adults through plastic reorganization of neurocognitive networks.

Table 10 provides a tentative overview of current hypothesis regarding the relation between psychosocial factors and dementia, interpretations the associations, and references of some studies where these hypotheses are being examined. Although the interpretations are described separately for reasons of simplicity in the table, they actually overlap in various ways [16].

Table 10. Overview of the current hypotheses concerning an association between psychosocial factors and dementia

Associated factor	Hypothesis	Interpretation of the association	Causality?	References
Depressive symptoms, leisure activities, social isolation	-	Merely preclinical symptoms	Reversed causality	Chen et al, 1999 [94]
Education	-	Detection bias	No causality	Tuokko et al, 2003 [126]
Education, mental activities, work complexity	-	Premorbid intelligence is the confounder	No causality	Whalley et al, 2000 [116]
Education, mental activities, work complexity	Cognitive reserve	Protection against functional consequences, but not against neuropathological lesions	No causality, only delay of clinical disease onset	Scarmeas & Stern, 2003 [77]
Education	Brain reserve	Protection against functional consequences, but not against neuropathological lesions	No causality, only delay of clinical disease onset	Katzman et al, 1993 [27]
Physical activity, SES- related lifestyles	Vascular hypothesis	Direct or indirect effect through atherosclerosis	Potentially in the causal pathway	Laurin et al, 2001 [81] Rovio et al, 2005 [80]
Social isolation, depression, stressful social ranking	Stress hypothesis	Effect through hippocampal atrophy	Partially causal component	Sapolsky, 2001 [127] Sapolsky, 2005 [128]
Education, mental activities, work complexity, physical activity	Neurogenesis Brain plasticity	Regeneration of neurons or reorganisation of neuronal networks	Partially causal component	Churchill et al, 2002 [124] Cabeza, 2002 [129]

CONCLUSIONS

The major findings of this thesis are summarised below.

Study I. Frequent engagement in mental, social, or productive activities in old age is inversely related to dementia incidence. Participation in these activities was assessed on average six years before dementia diagnosis. Stimulating activities that involve either mental or psychosocial components may act as stimuli to preserve cognition or hinder cognitive decline.

Study II. Low education is associated with increased risk of AD and is not mediated by adult SES or socioeconomic mobility. This is in agreement with the hypothesis of cognitive or brain reserve. Alternatively, these findings may partly reflect a detection bias, by which subjects with a low level of education tend to be clinically diagnosed with AD and dementia at an earlier point in time. It may also suggest that education-related factors acting in early-life are relevant. Our findings stress the importance of collecting data concerning early-life conditions, when studying dementia in old age.

Study III. Mental, physical, and social components of common leisure activities have a protective effect against dementia. A broad spectrum of activities, or activities that includes more than one of the mental, physical, and social components, appears to be more beneficial, than to be engaged in only one type of activity that includes only one of the components.

Study IV. Inactivity and depressive symptoms are independently associated with increased risk of developing dementia six years later. The most robust effect is detected for depressive symptoms. Inactivity, depressive symptoms, and social isolation, taken together, may substantially increase the risk of dementia in old age, and social isolation modifies the effect of the two other factors.

Study V Complexity of work with data and people is associated with lower risks of dementia and AD but the effects are largely explained by education. However, the association between education and AD/dementia is modified by the highest levels of complexity such as analyzing, coordinating, and synthesizing data. These levels of complexity with data are associated with lower risk even among subjects with low education.

The effect of exposure to cognitive stimulation through the life course is a main topic of interest in this thesis. The reserve hypothesis was first suggested as an explanation for the association between level of education and dementia risk [27] and further extended to take into account the possible beneficial influence of mental activity throughout the entire lifespan

[28,77]. The five studies in the thesis identified several sources of cognitive stimulation throughout the lifespan and indicated that 1) education above the elementary level; 2) higher levels of work complexity; and 3) frequent involvement in leisure activities all are related to reduced risk of dementia. This supports the recent suggestion by Richards and Deary, 2005[35] that "the reserve model applies across the life course, to cognitive development in childhood, as well as to adulthood and later life, recognizing that cognitive ability is modifiable at all stages of the life course."

Occupation-based SES at three different points in life (age 20, 40, and 60) was explored, showing an increased risk of dementia and AD associated with mobility patterns with low SES at 20 years. This indicates that early-life may have a specific impact on the risk of dementia in old age.

Social network and activities, loneliness, and low mood were investigated in old age but we did not have access to data concerning these variables in childhood or middle age. Psychosocial factors acting in old age were, however, available and were found to be associated to dementia risk in an inter-related way.

GENERALIZABILITY

No population is fully representative of all populations, and the unique characteristics of a specific group should be kept in mind when generalizing the main findings to different populations. The Kungsholmen Project cohort consisted of older individuals ($\geq$ 75 years), living in a geographically defined central area of Stockholm. One very special feature of the population is that it included only two persons who had been farmers in their main occupation. Kungsholmen was a distinctively urban area, but differed from other urban areas in Sweden in that there were higher proportions of pensioners, women, highly educated persons, and unmarried or divorced persons. However, it was fairly similar in age and gender composition and had comparable health care system as other parts of Stockholm [111]. Some caution is needed when generalizing some of the findings to, for example, younger persons or rural areas. Inference from studies carried out in this population may still be generalized to older urban populations in Western countries.

FUTURE DIRECTIONS

The five studies in this thesis will provide a basis for future exploration of factors acting at three different life periods using other statistical techniques like structural equation measurement models (SEM), which also take into account inter-correlations between the factors, when exploring the life course model for dementia risk.

Early-life factors may play a role in the development of AD and dementia. However, further data regarding conditions during childhood and adolescence is needed in order to fully evaluate this hypothesis. In a recently started data collection, The Swedish National Study of Aging and Care in Kungsholmen (SNACK), interview questions concerning occupation of parents, as well as economical and social problems during early-life are included. This will create new possibilities to illuminate this period in life in relation to diseases in old age such as dementia.

Several recent studies, like ours, have shown that an active and socially integrated lifestyle in late-life protects against dementia and AD. Nevertheless there are still remaining questions such as whether premorbid personality or intelligence may explain the reported associations.

In this thesis, working life was investigated from two major aspects: socioeconomic status and occupational complexity. Both these occupational factors need further investigation and should also be expanded to cover, for example, work stress as a putative risk factor for dementia.

Loneliness and low mood in old age was reported by almost a third of the investigated elderly. This condition should be further studied both in its own right and in relation to dementia and other diseases.

RELEVANCE

Scientific relevance

Our findings contribute to the understanding of etiopathogenic mechanisms involved in dementia development, and support the hypothesis that dementia is a multi-factorial disorder. The results further indicate that social factors acting at different life periods are relevant for dementia risk.

Public health relevance

Detecting preventable risk factors for dementia diseases is an important public health concern. Our findings concerning education suggest that good childhood circumstances in general, and schooling in particular, are not only important goals in themselves, but may also have consequences for reducing the risk of developing dementia later in life. Our results further indicate that engaging in activities that cover more than one of the mental, physical, and social components is more beneficial than to be engaged in only one type of activity. One simple implication for public health and community is to make different types of activities more accessible to elderly persons which may also reduce their risk of developing dementia.

Half our study population reported at least one of the following: inactivity, depressive symptoms, or limited/poor social network. In both clinical and survey settings, information about these risk factors can easily be obtained by a few interview questions. Positive answers to the questions should alert clinicians to the possibility of an increased risk of dementia.

Relevance for the individual

For the elderly individual, especially for the large group of elderly without many years of education, it is essential to know that there is evidence that an active and socially integrated lifestyle in late-life might protect against dementia. The increased dementia risk due to genetic predisposition and lifetime exposure to risk factors may still be modulated in late-life by psychosocial factors.

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APPENDIX A

Appendix A. (also available at http://www.usc.edu/dept/LAS/psychology/SCRAP).

Description of complexity scores as presented in the Fourth Edition of the Dictionary of Occupational Titles (US Department of Labor, Fourth Edition, Revised, 1991, pp. 1005-1007). Complexity of work is rated along three dimensions: data, people, and things.

Note. The scores were reversed to reflect higher complexity with higher scores and lower complexity with lower scores.

	DATA	*Information, knowledge, and conceptions, related to data, people, or things, obtained by observation, investigation, interpretation, visualization, and mental creation, data are intangible and include numbers, words, symbols, ideas, concepts, and oral verbalization.*
6	*Synthesizing*	Integrating analyses of data to discover facts and/or to develop knowledge concepts or interpretations.
5	*Coordinating*	Determining time, place, and sequence of operations or action to be taken on the basis of analysis of data; executing determinations and/or reporting on events.
4	*Analyzing*	Examining and evaluating data. Presenting alternative actions in relation to the evaluation is frequently involved.
3	*Compiling*	Gathering, collating, or classifying information about data, people, or things. Reporting and/or carrying out a prescribed action in relation to the information is frequently involved.
2	*Computing*	Performing arithmetic operations and reporting on and/or carrying out a prescribed action in relation to them. Does not include counting.
1	*Copying*	Transcribing, entering, or posting data.
0	*Comparing*	Judging the readily observable functional, structural, or compositional characteristics (whether similar to or divergent from obvious standards) of data, people, or things.
	PEOPLE	*Human beings; also animals dealt with on an individual basis as if they were human beings.*
8	*Mentoring*	Dealing with individuals in terms of their total personality in order to advise, counsel, and/or guide them with regard to problems that may be resolved by legal, scientific, clinical, spiritual, and/or other professional principles.
7	*Negotiating*	Exchanging ideas, information, and opinions with others to formulate policies and programs and/or arrive jointly at decisions, conclusions, or solutions.
6	*Instructing*	Teaching subject matter to others, or training others (including animals) through explanation, demonstration, and supervised practice; or making recommendations on the basis of technical disciplines.
5	*Supervising*	Determining or interpreting work procedures for a group of workers, assigning specific duties to them, maintaining harmonious relations among them, and promoting efficiency, a variety of responsibilities is involved in this function.
4	*Diverting*	Amusing others. (Usually accomplished through the medium of stage, screen, television, or radio.)

3	*Persuading*	Influencing others in favor of a product, service, or point of view.
2	*Speaking-Signalling*	Talking with and/or signalling people to convey or exchange information. Includes giving assignments and/or directions to helpers or assistants.
1	*Serving*	Attending to the needs or requests of people or animals or the expressed or implicit wishes of people. Immediate response is involved.
0	*Taking instructions-Helping*	Helping applies to "non-learning" helpers. No variety of responsibility is involved in this function.
	THINGS	*Inanimate objects as distinguished from human beings, substances, or materials; machines, tools, equipment, and products. A thing is tangible and has shape, form, and other physical characteristics.*
7	*Setting up*	Adjusting machines or equipment by replacing or altering tools, jigs, fixtures, and attachments to prepare them to perform their functions, change their performance, or restore their proper functioning if they break down. Workers who set up one or a number of machines for other workers or who set up and personally operate a variety of machines are included here.
6	*Precision Working*	Using body members and/or tool or work aids to work, move, guide or place objects or materials in situations where ultimate responsibility for the attainment for standards occurs and selection of appropriate tools, objects, or materials, and the adjustment of the tool to the task require exercise of considerable judgment.
5	*Operating-Controlling*	Starting, stopping, controlling, and adjusting the progress of machines or equipment. Operating machines involves setting up and adjusting the machine or material(s) as the work progresses. Controlling involves observing gages, dials, etc., and turning valves and other devices to regulate factors such as temperature, pressure, flow of liquids, speed of pumps, and reaction of materials.
4	*Driving-Operating*	Starting, stopping, and controlling the actions of machines or equipment for which a course must be steered, or which must be guided, on order to fabricate, process, and/or move things or people. Involves such activities as observing gages and dials; estimating distances and determining speed and direction of other objects; turning cranks and wheels; pushing or polling gear lifts or levers. Includes such machines as cranes, conveyor systems, tractors, furnace charging machines, such as handtrucks and dollies, and power-assisted machines such as electric wheelbarrows.
3	*Manipulating*	Using body parts, tools, or special devices to work, move, guide, or place objects or materials. Involves some latitude for judgment with regard to precision attained and selecting appropriate tool, object, or material, although this is readily manifest.
2	*Tending*	Starting, stopping, and observing the functioning of machines and equipment. Involves adjusting materials or controls of the machine, such as changing guides, adjusting timers and temperature gages. Turning valves to allow flow of materials, and flipping switches in response to lights. Little judgment is involved in making these adjustments.
1	*Feeding-Offbearing*	Inserting, throwing, dumping, or placing materials in or removing them from machines or equipment which are automatic or tended or operated by other workers.
0	*Handling*	Using body members, handtools, and/or special devices to work, move or carry objects or materials. Involves little or no latitude for judgment with regard to attainment of standards or in selecting appropriate tool, object, or material.

APPENDIX B

Dissertations from the Division of Geriatric Epidemiology and Medicine, Department of Neurotec, Karolinska Institutet, 1998–2005

1998

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

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

Bogdanovic Nenad. Towards a multifaceted approach in neuropathological diagnosis.

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

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

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).

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).

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

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

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

1999

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

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

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

Elffors Lars. Hip fractures – A European perspective.

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

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

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

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

von Euler Mia. Experimental spinal cord injuries – a histopathological, neurogical, and pharmacological study in the rat.

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

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

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).

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.

2000

Eriksson Charlotta. Region-specific expression of the interleukin-1 system in rat brain following endotoxin challenge and excitotoxic neurodegeneration.

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

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.

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

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

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

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

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

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

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

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

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

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).

Froelich Fabre Susanne. Genetic studies of frontotemporal dementia.

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

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

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

Sennvik Kristina. A study of the â-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.

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

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

2002

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

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).

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.

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

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

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

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

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

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

2003

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

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.

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.

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

Mulugeta E. Muscarinic M1 and M4 receptor subtypes in normal and pathological conditions in the central nervous system: Studies on human and animal tissues using subtype selective ligands.

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

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

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

2004

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

Chen Zhiguo. Excitotoxic neurodegeneration in mouse brain. Roles of immune cells and cytokines

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

Kostyszyn Beata. Studies of presenilin function in neurodegeneration and in human embryonic CNS during development

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

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

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

Ödlund Olin Ann. Nutritional and functional effects of energy-dense food in the frail elderly.

Flood Fiona. Alzheimer's disease-related amyloid precursor protein and presenilin genes: Normal function and pathophysiology.

Laudon Hanna. Functional domains in the Alzheimer's disease-associated presenilin 1 protein.

El-Bakri Nahid Karrar. Estrogen effects on different neurotransmitters in rat hippocampus: Implications for cognitive function.

2005

Adikari Sanjaya. Cytokine-modulated dendritic cell immunotherapy in autoimmune diseases.

Larsson Mauleon Annika. Care for the elderly – a challenge in the anaesthesia context.

Häggström Elisabeth. Municipal care for older people – experiences narrated by caregivers and relatives.

Kihlgren Annica. Older patients in transition – from home care towards emergency care.

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

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

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

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