The influence of social relationships and leisure activity on adult cognitive functioning and risk of dementia

Longitudinal Population-based Studies

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Umeå 2015
"Pappa. Du lyssnar aldrig och minns ingenting. Du borde forska på ditt eget minne"

- Jonathan, 2015-01-19
Acknowledgements

The past few years have been stimulating and exciting for me, and I have been given the opportunity to study in a pleasant working environment, for which I am very grateful. Although being a PhD student is not entirely associated with positive feelings, at least not closer to the end, such negative memories will most likely fade after I have crossed the finish line.

I would like to take the opportunity to thank several people who have helped me through these past few years. And even though forgetting is natural, I do apologize if I forget to mention some of those who have played an important role in this project.

First and foremost, I would like to give my deepest gratitude to my supervisors Michael Rönnlund, Anna Sundström, and Lars-Göran Nilsson. Your insightful comments, methodological knowledge, and just keeping me on track during these years is greatly valued. Thank you for being supportive. Further, thank you Michael Rönnlund for giving me confidence in the bowling alley, and Anna Sundström for your deep understanding about what a loss in a football game can do to one’s mood. You make a great team! Lars-Göran Nilsson, thank you for giving me the opportunity to be a PhD student, and, of course, to work with a fantastic database.

Thanks to all at the Department of Psychology and to those who have worked within the Betula study in previous years. I am grateful to have had so many fine colleagues. A special thanks to Maud, you are great. To all participants in Betula, without you there would be no thesis.

I am also very grateful to the Graduate School in Population Dynamics and Public Policy, and director Johan Lundberg, who over the years has given me the opportunity for international exchange, conference participation, and many interesting interdisciplinary workshops. This will be of great benefit to me in the future.

Annika Nordlund and Carola Wiklund-Hörnqvist, thank you for giving valuable feedback on an earlier draft of this thesis. I hope that you will enjoy the final version. Bo Molander and Peter Hassmén, thank you for your valuable comments on the mid-seminar.

Bo Molander, you have been a great support and friend since my arrival at Umeå University in 2001 (although the first meeting was a shock). Without you, I would most certainly not have been a PhD-student. Thank you for giving me my current interest for research. Eternally grateful. Carola and Patrik, since 2008, we have followed each other and shared many interesting discussions, to say the least. I have very much appreciated these chats. I enjoy both of your personalities.

I am also thankful that I have made many friends within the PhD group. Thank you Susanne, Inga, Nina, Erik M, Erik L, Erika S, Erica E, Eva P, Johan, Robert, Helen, Hanna, Stefan B, Anna-Maria, Carola, Petra, Linus,
Ingrid, Stenling, Esther, Elisabeth, Olov, Olympia, Marius, and Markus for these years (hope I haven't missed anyone). The atmosphere within the PhD group has been very good. I hope this continues. Anna-Maria, you're a very kind person and I really like your strong belief that all people can achieve their goals if they work hard enough. Petra, I enjoyed being an internal reviewer at your final seminar. Good luck with far transfer, I keep my fingers crossed. Esther, it was great fun in Barcelona, a real highlight. Stenling, thank you for working for a healthy environment for our sports-active children. Marius, please teach me how to act. Linus, intolerance is an important aspect also for a king. Erik L, why a playoff beard when you never experience it? Olov, there can be only one, let it grow. Markus, let's go fishing instead of “always walking alone”. Elisabeth, I’ve tried to be a good mentor, but I admit that being frank was not always easy. Eva P, Kelly McGillis says “Hi”. I'll save the rest for later. All my respect to you guys.

Stefan H. & Ulrich, what about Patrick Thistle? By the way, Stefan, you are a good sport, looking forward to theory and practice. Gelfgren, competitions are fun, and even more fun if everyone is given the chance to win. Markus, Jessica, and Erik M, LA was a great experience. Maybe "Sweet Home Chicago" next time? We’ll see.

Family and friends, I know that I have been remiss in keeping in touch. Forgive me for my physical and mental absence. I will improve. Just know that I appreciate you all very much. Linda, my wife, thank you for all your encouragement and endless support. Love you. My sons, William and Jonathan, you are most important to me. Please don’t forget.

Umeå, April 2014
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Study I
Study II
Study III
Abstract
Today, as we live longer, dementia diseases are becoming more prevalent around the world. Thus, further knowledge of how to maintain levels of cognitive functioning in old age and how to identify factors that postpone the onset of dementia are of acute interest. Lifestyle patterns and social life are important aspects to consider in this regard.

This thesis includes three studies. In Studies I and II, data from the Betula prospective cohort study were examined. Betula is a population-based longitudinal project that started in Umeå, Sweden, in 1988. Study I investigated the association between participation in various leisure activities in old age (≥65 years) and risk of incident all-cause dementia. Analyses of the total follow-up time period (15 years) showed that higher levels of “Social” and “Total” leisure activity were associated with decreased risk of dementia. In Study II, the aim was to investigate the association between various aspects of social relationships in old age (≥65 years) and risk of incidents of all-cause dementia and Alzheimer’s disease. Results showed that over the total follow-up period (16 years) higher values on the relationship index were associated with reduced risk of both dementia and Alzheimer’s disease. Visiting/visits of friends and acquaintances more than once a week was related to decreased risk for all-cause dementia, but not for Alzheimer’s disease. However, in neither Study I nor II did any of these factors alter the risk of all-cause dementia or Alzheimer’s disease when near-onset dementias were removed from the analyses (Study I, up to five years; Study II, up to three years).

Study III included participants who had taken part both in the Betula study and the Västerbotten Intervention Programme. The aim was to investigate the association between social network size and cognitive ability in a middle-aged (40–60 years) sample. The idea was that if social network size can moderate negative age-related influence on memory functions, it might also put an individual on a cognitive trajectory that is beneficial in old age. Results from longitudinal analyses showed that baseline network size was positively related to five-year changes in semantic memory and with changes in both semantic and episodic memory at the ten-year follow-up. Social network size was unrelated to changes in visuospatial performance.

Taken together, enrichment factors measured in old age (≥ 65 years) did not alter the risk of all-cause dementia or Alzheimer’s disease when near-onset dementias were removed from the analyses. These results might reflect protective short-term effects or reverse causality, meaning that in the prodromal phase of dementia individuals tend to withdraw from activity. Social network size in middle age (40-60 years), however, appears to have beneficial long-term effects on cognitive functioning. The results highlight the importance of long follow-up periods and the need to adjust for the
influences of reverse causality when investigating the impact of a socially and mentally active life on cognitive functioning.
List of papers


Sammanfattning

Som en konsekvens av att vi lever längre blir demenssjukdomar allt vanligare runt om i världen. Ökad kunskap om hur vi bibehåller god kognitiv funktion i åldrandet samt identifierar faktorer som kan skjuta upp tidpunkten för insjukande i demenssjukdomar är därför av stor vikt. Livsstilsmönster och socialt liv är viktiga aspekter att beakta i sammanhanget.


I Studie III inkluderades individer som deltagit både i Betulaprojektet och i Västerbottens hälsoundersökning. Data från båda studierna finns länkad i Linne-databasen. Syftet var att undersöka sambandet mellan storlek på socialt nätverk och kognitiv förmåga i en medelålders (40-60 år) population. Tanken var att om nätverksstorlek kan modifiera negativa åldersrelaterade kognitiva förändringar hos denna åldersgrupp, kan det potentiellt också ha en långvarig effekt som blir gynnsam i hög ålder. Resultaten visade att större socialt nätverk vid baslinjemätning var positivt relaterat till förändring i semantiskt minne över fem år. Över tio år var det relaterat till förändring både i semantiskt och episodiskt minne. Storleken på det sociala nätverket hade inte något longitudinellt samband med visuospatial förmåga.

Sammantaget visar resultaten att faktorer som undersöks vid hög ålder (≥65 år) inte har något samband med demens eller Alzheimers sjukdom då de som insjuknat strax efter baslinjemätning exkluderats från analyserna. Detta kan eventuellt indikera skyddande korttidseffekter, men det kan också spegla omvänd kausalitet, det vill säga att personer i ett
förstadium till demens blir mindre aktiva. Storleken på det sociala nätverket i medelåldern (40-60 år) tycks emellertid kunna ha långsiktiga effekter på vissa kognitiva förmågor. Resultaten belyser vikten av långa uppföljningsperioder, samt justering för effekter av omvänd kausalitet, när effekter av ett socialt och mentalt aktiv liv undersöks i relation till kognitiv funktion.
Introduction

Today, as people live longer, dementia is becoming more prevalent around the world. According to the World Alzheimer Report (2010), 35.6 million people currently suffer from dementia. This number is estimated to increase to 65.7 million by 2030 and reach 115.4 million by 2050. Hence, advances in knowledge of how to maintain levels of cognitive functioning in old age and how to identify factors that postpone the onset of dementia diseases are of acute interest, not only from an individual viewpoint, but also from a societal perspective.

In the last decade, a variety of factors have been suggested as playing a role in cognitive functioning and risk of incident dementia. Although neurostructural factors established early in life (Raz & Rodrigue, 2006) and genetic factors (Gatz et al., 2006) have been shown to be critical, environmental influences are important to take into account. It has, for example, been suggested that engagement in various leisure activities can be beneficial for cognitive functioning. Reviews suggest that participation in mental, intellectual, and social activities in adulthood and old age can be helpful in reducing the risk of cognitive decline and to decrease the risk of dementia (see Fratiglioni, Paillard-Borg, & Winblad, 2004; Stern & Munn, 2010; Wang, Xu, & Pei, 2012). Another related factor assumed to affect cognitive functioning is social relationships. Some prior studies have, for instance, found that having a larger number of social relationships and/or having more frequent contact with family and friends might be beneficial for cognitive functioning and might reduce the risk of dementia (e.g., Bennett, Schneider, Tang, Arnold, & Wilson, 2006; Crooks, Lubben, Petitti, Little, & Chiu, 2008; Fratiglioni et al., 2004; Zunzunegui, Alvarado, Del Ser, & Otero, 2003).

Associations found with leisure activity and social relationships are often assumed to be in accordance with the cognitive reserve hypothesis, suggesting that intellectual stimulation can reduce decline in cognitive functioning, decrease the risk of dementia, and provide resources to function normally even in the presence of dementia pathology (Scarmeas & Stern, 2003). Engagement in leisure activity and social relationships can affect cognitive functioning through other paths than cognitive stimulation, though. An engaged lifestyle can, for example, lower the risk of stress (e.g., Iwasaki, Mactavish & Mackay, 2005; Ozbay et al., 2007) and depression (e.g., Glass, de Leon, Bassuk, & Berkman, 2006; Jang, Borenstein, Chiriboga, & Mortimer, 2005), factors that have been associated with both cognitive functioning (for stress, e.g., Bremner et al., 1993; Golier et al., 2002, for depression, e.g., Sachs-Ericsson, Joiner, Plant, and Blazer, 2005; Zelinski & Gilewski, 2004) and risk of dementia (for stress, e.g., Johansson et al, 2010; for depression, e.g., Jorm, 2001; Ownby, Crocco, Acevedo, John &
Loewenstein, 2006). It could also be the case that lowered activity level is a consequence of, rather than a risk factor for, cognitive impairment (Pillai & Verghese, 2009). More knowledge about the extent to which these factors might generate broader effects and postpone cognitive decline and/or dementia diseases is required. Most researchers agree that longitudinal studies are the best way to examine what factors influence intraindividual cognitive changes in old age. Longitudinal studies also make it possible to measure exposure variables prior to the development of dementia diseases (Hertzog, Kramer, Wilson, & Lindenberger, 2008).

The overarching aim of this thesis was to investigate the relationships between leisure activity and social relationships and longitudinal changes in memory functioning and/or risk of dementia. All three studies were population based and included longitudinal follow-up. Studies I and II focused on an elderly population (65-95 years), and Study III targeted middle-aged adults (40-60 years). The first two studies were based on data from the Betula prospective cohort study (Nilsson et al., 1997, 2004), whereas the third study included data from both the Betula study and the Västerbotten Intervention Programme (Norberg, Wall, Boman, & Weinehall, 2010).

The introduction to this thesis provides a background of the empirical studies. Following the introduction, interindividual differences in cognitive ability and risk of dementia, and unexplained causes for variance, will be discussed. Next, I will introduce aging theories designed to explain causes of age-related differences in cognitive functioning and/or risk of dementia. The cognitive reserve hypothesis, in focus in all three studies, will then be introduced. After that, the enrichment factors investigated in the thesis—leisure activities and social relationships—will be discussed in light of the cognitive reserve hypothesis. However, as will be argued, these factors can also be linked to cognitive functioning through pathways other than the cognitive reserve. Also, the possibility of a reverse relationship between activity level and cognitive functioning, as well as other aspects that affect the ability to live an active life, will be elaborated. An overview of memory and dementia, and the specific constructs related to these concepts, will then be introduced and discussed from a life-course perspective. The differences between “normal” cognitive aging and dementia will also be highlighted. Finally, other factors assumed to influence cognitive functioning and that were considered in the empirical studies will be presented.

The basis of individual differences in cognitive functioning in old age

There is a great need to explore what factors are associated with cognitive functioning and the risk of dementia. Although declines in cognitive functioning are observed with aging, it should be noted that there are large
variations between individuals, and much of these interindividual differences in level and rate of change of cognitive functioning remain unexplained. Important questions are (1) what factors cause these individual differences, (2) to what extent these factors are associated with the magnitude of age-related decline, and (3) to what extent these factors influence the risk of dementia.

In cross-sectional data, considerable interindividual variability in cognitive performance is observed among older adults. By presenting overall individual performance based on all memory tests within the Betula study (Nilsson et al., 1997; 2004), Habib, Nyberg, & Nilsson (2007) demonstrated that the variance in test performance is large in all age groups (see Figure 1). There are individuals in the upper end of the age spectrum that perform at a level of many younger adults, and there is a relatively large proportion among those 70 years and older who perform above the average level of 50–65 year olds. Based on longitudinal analyses, the authors also found that a minority of the older adults (70-85 years) not only performed at a high level, but they maintained their level of performance over time. The authors found that years of formal education was one factor that predicted this stability.

Figure 1. Principle coordinates of cognitive performance for every participant in the Betula study as a function of age based on data collected during the second occasion between 1993 and 1995. The vertical line shows the mean of middle-aged subjects (50–65 years). Reprinted with the permission of Taylor and Francis Group.
Although high initial levels of cognitive performance are advantageous, these do not automatically guarantee protection against cognitive deficits from a long-term perspective. Wilson et al. (2002b) followed participants over a six-year period to investigate changes in several cognitive abilities. The authors found that changes, in general, occur in most cognitive domains and that change is more rapid in older people. However, the results also showed that baseline ability was not a good predictor of the rate of longitudinal change. The authors emphasized that although there are large individual differences in cognitive ability, person-specific factors might primarily contribute to changes. Moreover, in addition to major differences in terms of baseline ability and rate of change, there are also individual differences in cognitive ability in the presence of dementia pathology (Stern, 2002). A number of studies have shown that people who are considered as non-demented, based on measures used in longitudinal studies, often fulfill the pathological criteria of dementia at autopsy (Crystal et al., 1988; Morris et al., 1996; Price & Morris, 1999).

Models of cognitive aging
There are several models proposed to account for age-related deficits in cognitive test performances, and some of these will be considered here.

One model that attempts to account for differences in cognitive ability is the processing speed theory. This model assumes that a decline in a general factor—processing speed—can account for most of the age-related decline in a variety of cognitive tasks (Salthouse, 1996), for example, in episodic memory (e.g., Hultsch, Hertzog, & Dixon, 1990; Salthouse, 1993). Changes in processing speed are believed to be a consequence of a general slowing of the nervous system that comes with advanced age. However, it should be noted that more recent longitudinal data provide little support for the speed hypothesis (Sternäng, Wahlin, & Nilsson, 2008).

Another model of cognitive aging is the common cause hypothesis (Baltes & Lindenberger, 1997). This hypothesis suggests that a decrease in a common factor can predict age-related deterioration both in cognitive and non-cognitive processes. The cognitive deficits can include all higher order cognitive functions. The common cause hypothesis suggests that losses in a variety of cognitive functions are significantly connected with losses in other processes such as vision, auditory, and physical functioning. However, as with the processing speed theory, longitudinal data do not lend strong support for the common cause hypothesis (see Sternäng, Jonsson, Wahlin, Nyberg, Nilsson, 2010).

Another concept used in research of cognitive aging is "successful aging", although it does not exclusively refer to the cognitive aging process. The concept itself is rather an umbrella term, and according to Rowe & Kahn (1999) “successful aging” contains three main components. The first includes
low probability of diseases and disabilities. The second component refers primarily to the ability to have "engagement with life," while the third component concerns mental and physical function. Because "successful aging" is defined in many different ways in the literature, and often reflects what the researcher is interested in (Bowling, 2005), it should probably not be regarded as a theory, but rather as an attempt to include the importance of sufficient cognitive function as a vital aspect of aging.

Another model, often mentioned in the same body of research as "successful aging", is "selective optimization with compensation" (Baltes, 1990; Riediger, Freund & Baltes, 2005). According to this theory the subjective experience of aging is essential, and the elderly can retain function despite cognitive decline by utilizing most of their preserved functional abilities.

The notion that "mental exercise" can enhance general cognitive ability has been put forward for at least a century (see Foster & Taylor, 1920; Jones & Conrad, 1933; Thorndike, Tilton, & Woodyard, 1928), and a concept that is widely used in the literature today is "use it or lose it" (Swaab, 1991). This perspective assumes that mental stimulation can generate broader effects on cognitive function and that we maintain cognitive function and, possibly, also reduce the risk of dementia by keeping mentally active. The idea that we should continue to keep mentally active to prevent cognitive decline is inherent in variants of the cognitive reserve hypothesis, which is in focus in this thesis. The concepts are overlapping, but the cognitive reserve hypothesis often relates to the idea that an individual should be mentally active throughout their lifespan in order to build up a reserve of cognitive ability. The "use it or lose it" concept is rather an umbrella term that might represent either the ideas of the reserve hypothesis or the use-dependency theories, which makes the assumption that cognitive activity in later life is sufficient to maintain good cognition in old age (Almond, 2010). Furthermore, as will be noted in the next section, the term cognitive reserve was based on the notion that cognitive stimulation could provide resources to cope with dementia pathology (Scarmeas & Stern, 2003).

Similar to these theories is the "disuse" hypothesis that posits that changes that occur later in life, such as retirement, loss of loved ones, and/or loneliness, can in turn cause a loss of cognitive stimulation (for example, less need for problem-solving), that in turn can cause reduction in fluid abilities (e.g., Christensen et al., 1996; Paggi & Hayslip, 1999; Schooler, Mulatu, & Oates, 1999). Although the concepts overlap, the cognitive reserve terminology will be used in this thesis because we considered it well suited for investigating long-term effects of cognitive stimulation. Further, as previously noted, the cognitive reserve hypothesis aims to explain how cognitive stimulation can provide resources to cope with dementia pathology (Scarmeas & Stern, 2003), an outcome in focus in this thesis.
The cognitive reserve hypothesis

In recent years, as a consequence of increased scientific interest in prevention and methods of treatment for dementia, the cognitive reserve hypothesis has received considerable attention. The hypothesis (or model) is based on evidence showing that intellectual enrichment can decrease the risk of dementia and promote the build-up of resources to cope with dementia pathology (Scarmeas & Stern, 2003). The concept is regularly defined as our capacity to efficiently use our brain networks and cognitive components (Stern, 2002), but the concept also refers to larger neural capacity and the ability to recruit additional brain regions to compensate for age-related cognitive changes (Tucker & Stern, 2011). An individual’s cognitive reserve is not believed to be static, but is considered, at least partly, to be modifiable over the entire life course. Thus, if we stimulate the brain enough, we might build up cognitive networks that become valuable as areas of the brain start to deteriorate (Hultsch, Hertzog, Small, & Dixon, 1999; Scarmeas & Stern, 2003; Katzman, 1993). Findings also suggest that substantively complex tasks performed even in old age can create a capacity to deal with the intellectual challenges from the environment (Schooler & Mulatu, 2001).

The cognitive reserve attempts to account for the fact that some individuals with extensive neuropathology associated with dementia show little cognitive decline when others with similar pathology show marked deficits (Stern, 2002; Esiri & Chance, 2012). According to the model, individuals have different amounts of reserve capacity, and as the brain starts to deteriorate in later life the person with a higher reserve capacity is less affected by the deterioration. It should be noted, however, that when using pathology as a reference, little is said about reserve capacity before the onset of pathology.

Although the cognitive reserve is frequently considered as an active model, meaning that it can be influenced by intellectual enrichment, passive models of the reserve should also be highlighted. The passive models are often linked to the brain reserve concept (Katzman, 1988; 1993). A traditional view of the passive models is that the reserve capacity represents the hardware of the brain, and they are often linked to neuroanatomical measures such as brain size and/or the number of neurons or synapses. This perspective also emphasizes biological differences as one possible cause of reserve capacity, although it does not exclude the influence of an engaged lifestyle. Even though individuals with higher brain reserve allow a larger loss of “hardware” before cognitive impairment is manifested, an engaged lifestyle might modify the pathology associated with cognitive impairment or dementia (Valenzuela, 2008). Regardless of whether active or passive models are considered, cognitive stimulation might cause physiological changes to the brain.
Effects of cognitive stimulation on the brain
The first assumption of the cognitive reserve model, i.e., the more efficient use of brain networks, can refer to enhanced synaptic activity or the generation of more efficient circuits of synaptic connectivity as the result of cognitive stimulation. The second assumption, i.e., better use of alternative networks, refers to the ability to shift operations to other brain circuits (Scarmeas & Stern, 2003). This notion of brain plasticity is often considered the basis of cognitive reserve theory (Lövdén, 2010).

Valenzuela, Breakspear, and Sachdev (2007) reported in their review that enrichment factors (e.g., various factors believed to be mentally stimulating) can be beneficial not only to brain plasticity, but might also promote some neurotrophic factors. Enrichment can increase neurogenesis in the hippocampus, an area that is important for learning and memory functioning. Intellectual enrichment has also been related to nerve growth, which is important for regulation of cell body size and dendritic and spine density, and further plays an important role in the pathology of Alzheimer’s disease (AD). Furthermore, it is possible that cognitive stimulation has an impact through breakdown of amyloid plaque, which is associated with dementia progression. Moreover, in AD the density of neurofibrillary tangles is greater, often in the prefrontal cortex and hippocampus. Individuals with higher cognitive capacity earlier in life have been shown to have reduced densities of tangles. Thus, one interpretation could be that the cognitive reserve, as measured by prior cognitive capacity, is associated with the spread of dementia pathology in old age (Esiri & Chance, 2012). In addition, it has been found that education and work complexity are related to more complex dendritic patterns (Valenzuela et al., 2007) and that cognitive reserve indicators (e.g., intellectual activities) are associated with brain metabolic activity and regional brain blood flow (Solé-Padullés et al., 2009). However, although it has been suggested that cognitive stimulation might affect the brain in many different ways, the architectural neural basis for the cognitive reserve is still not well understood (Esiri & Chance, 2012).

Effects of leisure activity
Leisure activities can be defined as activities that individuals engage in for enjoyment or well-being that are independent of work or activities of daily living (Verghese et al., 2006). According to the “activity theory” (Havighurst, 1961), engagement and maintenance of activity levels are important to maintain life satisfaction. In the last decades, increased interest has been directed towards the relationship between leisure activity and cognitive functioning. Many of these studies have focused on the effects of cognitive stimulation in later life (≥65 years of age) and found that frequent or increased participation in mental, social, and/or productive activities is associated with reduced risk of dementia and/or cognitive decline (e.g.,
Karp, Paillard-Borg, Wang, Silverstein, Winblad, & Fratiglioni, 2006; Paillard-Borg, Fratiglioni, Winblad & Wang, 2009; Scarmeas, Levy, Tang, Manly & Stern, 2001; Verghese et al., 2003; Wang, Karp, Winblad & Fragtiglioni, 2002; Wilson et al., 2002a; Wilson et al., 2002b). In a similar vein, studies of cognitive training (e.g., task-switching, complex video games, divided attention) have confirmed that older adults can improve their cognitive performance following participation in intensive training programs (Hertzog et al., 2008). Furthermore, and in line with the cognitive reserve hypothesis, it has been found that engagement in leisure activities in early and middle adulthood might decrease the risk of cognitive decline and dementia in old age (e.g., Carlson, Helms, Steffens, Burke, Potter, & Plassman, 2008; Crowe, Andel, Pedersen, Johansson & Gatz, 2003; Friedland et al., 2001; Fritsch, Smyth, Debanne, Petot & Friedland, 2005; Glei, Landau, Goldman, Chuang, Rodríguez, & Weinstein, 2005; Lindstrom et al., 2005). Kåreholt, Lennartsson, Gatz, and Parker (2011) found that mental (e.g., reading, playing a musical instrument), socio-cultural (e.g., study circles, theatre), and political activities (e.g., political speeches, written articles) undertaken between 46-75 years of age were positively associated with cognitive functioning 20 years later in life. Taken together, a number of reviews also propose that engagement in leisure activities over the life span can be beneficial to maintaining cognitive ability and to reducing cognitive decline and dementia risk (see, e.g., Fratiglioni et al., 2004; Stern & Munn, 2010; Wang et al., 2012).

While there are studies indicating that a higher activity level benefits cognition, it should be noted that there are several studies finding no relationship between leisure activity and cognitive functioning and risk of dementia (see, e.g., Akbaraly et al., 2009; Aartsen, Smits, van Tilburg, Knipscheer & Deeg, 2002; Saczynski et al., 2006; Wilson et al., 2002a; Wang et al., 2006), and some researchers question the notion that keeping mentally active prevents age-related decline (Salthouse, 2006). However, there is a possibility that engagement in leisure activities might promote cognitive functioning through other pathways. Although several of these factors (e.g., stress, depression) will be discussed in more detail later in this thesis, they will briefly be discussed here as possible mechanisms that can modify the effects between leisure activity and cognitive functioning.

Other pathways from leisure activity to cognitive functioning
Apart from a direct link via cognitive stimulation, it could be that engagement in leisure activities affects cognition through other pathways. For example, an engaged lifestyle could potentially reduce the risk of heart attack/cardiovascular problems, stroke, diabetes, and high blood pressure (hypertension), factors that have all been negatively associated with cognitive functioning (see Anstey & Christensen, 2000; Launer et al., 2000;
Qiu, Winblad, Viitanen & Fratiglioni, 2003). Furthermore, higher levels of engagement in leisure activities have been related to lower risk of depression (Glass et al., 2006) and stress (Iwasaki et al., 2005), factors that have also been associated with cognitive functioning (for stress, e.g., Bremner et al., 1993; Golier et al., 2002, for depression, e.g., Sachs-Ericsson, et al., 2005; Zelinski & Gilewski, 2004) and dementia (for stress, e.g., Johansson et al, 2010; for depression, e.g., Jorm, 2001; Ownby et al., 2006). An engaged lifestyle might also give access to a larger social network that in turn might be beneficial to the individual's overall health (e.g. mental and physical). When interacting with others, we tend to adapt to social norms (Holt-Lunstad, Smith, & Layton, 2010) and might, therefore, change our habits regarding, for example, smoking, alcohol use, and physical activity, all of which are factors that can influence cognitive functioning. Thus, because leisure activities might affect different health outcomes, they might also affect cognitive functioning indirectly.

Reverse causality and other factors related to patterns of leisure activity
Illnesses and poor mental and physical health that might come with higher age can reduce the possibilities of an active lifestyle (Bukov, Maas, Lampert, 2002), and it has been found that with advanced age more time is generally devoted to daily self-care activities that in turn reduces the time for leisure activities (Horgas, Wilms, & Baltes, 1998; Lawton, Moss, & Fulcomer, 1987). Furthermore, with higher age it often takes longer to solve intellectual challenges (Clay et al., 2009; Salthouse, 1996). Hence, changes in cognitive ability could affect patterns of leisure activity directly (Hultsch et al., 1999). It is possible that the elderly withdraw themselves from certain leisure activities because more time (and cognitive resources) is needed to undertake them, and activities that used to be associated with well-being and satisfaction instead cause frustration and become a reminder of lost abilities. Furthermore, and most importantly, activity level can possibly also signal preclinical symptoms of dementia because the prodromal phase is known to be long (Amieva et al., 2008). Thus, at least in some cases, reduced engagement might be a consequence, rather than a risk factor, for cognitive impairment. Hence, the possibility of so-called reverse causality should be considered when investigating the relationship between leisure activity and cognitive functioning/dementia. Nevertheless, many studies within this field have used a relatively short follow-up period, often less than five years, which minimizes the possibility to adjust for reverse causality (e.g., Akbaraly et al., 2009; Fabrigoule et al., 1995; Wilson et al., 2002a). Only a limited number of studies have adjusted for reverse causality by having a time period between measurement of social relations and the first cases of dementia (e.g. Paillard-Borg et al., 2009; Wang et al., 2002)
Activity patterns, however, might not only be a consequence of cognitive status. After retirement, the elderly in general have more spare time that can be allocated to leisure activities (Gauthier & Smeeding, 2001). Thus, elderly individuals with sufficient physical and cognitive capacity can be motivated to increase their engagement in leisure activities.

Another factor that might relate to activity patterns is education. Individuals with higher education are more likely to be active in social and productive activities than the less educated (Bukov et al., 2002). Furthermore, higher levels of education in general result in higher income and higher socio-economic status, which are factors that might influence the choice of activities. Furthermore, although engagement in certain leisure activities can benefit access to social networks, it might also be the other way around such that people with larger networks tend to be more active (Vance, Ross, Ball, Wadley, & Rizzo, 2007). Gender differences have been observed in regard to leisure activities, and women more often tend to engage in more sedentary and indoor (often home-based) activities, whereas men often prefer physical activities (O’Brien Cousins, 1998).

There might be cohort effects regarding the choice of leisure activities, and lifestyle changes provide a variety of new activities that might attract new generations. Furthermore, differences in earlier stages of life (e.g., socio-economical differences) may have provided more diverse opportunities and interests in leisure for different individuals. It has been suggested that new generations are more active compared to former generations due to differences in resources earlier in life (Huber & Skidmore, 2003). Even if there is a large variety in the number of activities nowadays, selections made by the elderly are often restricted to factors such as personal economics, culture, and climate (Mollenkopf, Marcellini, Ruoppila, Széman, & Tacken, 2005).

**Effects of social relationships**

Social relationships is a broad term that can be used to refer to structural aspects of an individual’s social life (e.g., marital status, living status, network size, or contact frequency) as well as functional aspects (e.g., received or perceived emotional support) of social relations (Holt-Lunstad et al., 2010). Although various other overlapping concepts such as social engagement, social integration, social support, and social network are used in the literature (Berkman, Glass, Brissette, & Seeman, 2000), social relationships can be regarded as an umbrella term. Furthermore, the social network is considered as the matrix of social relationships that individuals are tied to (Peek & Lin, 1999).

It has been suggested that characteristics of an individual’s social relations can be regarded as indicators of intellectual enrichment and that having a rich social life can be cognitively challenging because conversation
with others taps several cognitive components, including memory and attention (Ybarra et al., 2008). Thus, preserving social connections and being socially active has not only been regarded as an indicator of an active lifestyle (Bassuk, Glass, & Berkman, 1999), but it has also been found to be related to factors such as illness frequency, immunological functioning, happiness, depression, well-being, heart disease, morbidity, and mortality (Rook et al., 2007; Barger, 2013; Krumholz et al., 1998; Mookadam & Arthur, 2004; Seeman & Crimmins, 2001; Tay, Tan, Diener, & Gonzalez, 2013; Uchino, Cacioppo, & Kiecolt-Glaser, 1996), with both the level and change in cognitive functioning (e.g., Barnes, Mendes de Leon, Wilson, Bienias, & Evans 2004; Bassuk et al., 1999; Beland, Zunzunegui, Alvaro, Otero, & Del Ser, 2005; Ertel, Glymour, & Berkman, 2008; Fratiglioni et al., 2004; Holtzman et al., 2004; Lövdén, Ghisletta, & Lindenberger, 2005; Zunzunegui et al., 2003), and with reduced risk of all-cause dementia and AD (e.g., Bickel & Cooper, 1994; Crooks et al., 2008; Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Helmer et al., 1999). However, exceptions to these patterns exist (see Beard, Kokmen, Offord, & Kurland, 1992; Glei et al., 2005; Holwerda et al., 2012; Seeman et al., 2001).

Bennett et al. (2006) found that social network size modified the association between AD pathology and cognitive function. Their study showed that cognitive function was higher for participants with larger network size even in the presence of AD pathology—a result that is in accordance with the cognitive reserve hypothesis (Scarmeas & Stern, 2003, Stern, 2002)—and this suggests that a larger social network provides better resources to cope with dementia pathology.

Despite the interest in the influence of social factors in old age, limited attention has been paid to the influence of social relations and cognitive functioning in midlife (e.g., Green, Rebok, & Lyketos, 2008; Seeman et al., 2011; Ybarra et al., 2008). Middle age should be of special interest because it is characterized as a period of decreasing network size (Wrzus, Hänel, Wagner, & Neyer, 2013), a change that could possibly exert a negative influence on cognitive functioning. The potentially protective effects of midlife social relations have also not been well studied regarding cognitive impairment and risk of dementia in old age (for exceptions see, Håkansson et al., 2009; Saczynski et al., 2006). As for leisure activities, social relations might promote cognitive functioning through other pathways than cognitive stimulation. Although several of these factors will be discussed in more detail later in this thesis, they will now be briefly discussed here.

**Other pathways from social relationships to cognitive functioning**

Even if positive associations between social relationships and cognitive functioning can be explained by the cognitive reserve model (Scarmeas &
Stern, 2003; Stern, 2002), it is possible that social relations can affect cognition through other pathways. Social relations can provide support that can be informational, emotional, and/or more tangible and thus provide an individual with useful resources to cope with stressors in life (Holt-Lunstad et al., 2010; Ozbay et al., 2007). Furthermore, it is well known that regulation of moods, emotions, and feelings of control are psychological processes that can be linked to social relationships (Uchino, 2006). Thus, social relations might be important for cognition indirectly because—as will be presented in later chapters—cognitive abilities (Sands, 1981–1982; Vondras, Powless, Olson, Wheeler, & Snudden, 2005) and risk of dementia (Johansson et al., 2010) can be affected by psychological stress. Similarly, individuals with larger social resources have reduced risk of depressive symptoms (Jang et al., 2005), a factor that has also been associated with cognitive decline (e.g., Sachs-Ericsson et al., 2005; Zelinski & Gilewski, 2004) and the risk of dementia (Jorm, 2001; Ownby et al., 2006). Furthermore, social relations can encourage a healthier lifestyle (Lewis & Rook, 1999) that in turn might influence cognitive ability (e.g., healthier food habits, consistent exercise, not smoking) because when interacting with others we tend to adapt social norms or engage in activities that promote a healthier lifestyle (Holt-Lunstad et al., 2010).

Reverse causality and other factors related to patterns of social relations

It is important to point out that reduced engagement in social relations in old age, just as for leisure activities, might be a consequence of cognitive impairment (see Pillai & Verghese, 2009). Furthermore, individuals, at least in the prodromal phase of dementia, are probably less able to participate in, or are less interested in engaging in, social relationships and thus show a pattern of social withdrawal. Although there is an obvious risk of reverse causality influencing the results when investigating the association between social relations and dementia, several studies have used a relatively short follow-up period—often not more than five years—after late-life measurement of social relations (e.g., Beard et al., 1992; Crooks et al., 2008; Helmer et al., 1999; Holwerda et al., 2012). Even if an adjustment for reverse causality are motivated in studies investigating the association between social relationships and cognitive functioning, only a limited number of studies have a sufficiently long time frame between baseline measurement and the occurrence of dementia (e.g., Amieva et al., 2010; Håkansson et al., 2009; Saczynski et al., 2006).

Other factors, however, could also influence patterns of social relationships. Deterioration in physical health might mean that more time is needed for daily self-care activities, a limitation that might reduce the time for social interactions (Horgas et al., 1998; Lawton et al., 1987). The loss of
close relationships becomes more common at older ages (e.g., death of a spouse or friends) that can also reduce the number of social contacts. Even though it is common to have a smaller social network size in old age, older adults appear to play an active role in managing their social relationships, which in turn might also affect their network size. Compared to younger individuals, the elderly often choose to interact with individuals who can bring them emotional reward and support because this, generally, optimizes well-being (Rook et al., 2007). In the same vein, it has been found that the elderly are usually more focused on attaining a desired emotional state than their younger counterparts (Gurung et al., 2003), and it is not uncommon that long-term bonds (e.g., with a spouse or near friends) that give more support become more important. It has been found that in aging the range of interaction partners often becomes narrower and more confined to an “inner circle” often consisting of familiar partners, thus reducing the total network size. The number of close ties, however, can still be comparable to that of younger persons. Thus it is not certain that decreases in network size mirror threats to well-being or health; rather, it can represent how the elderly try to preserve health and well-being (Rook et al., 2007).

Memory systems
The memory systems will be introduced in the following section, but first a brief background on the concept of memory will be given. The word “memory” is frequently used in everyday life, and people often refer to their own memory as a thing or device in terms of how well it works, and it is often considered as place holding information of past events (Wagoner, 2012). Morris (2007) describes perspectives of how memory is thought of in the neurosciences, which to some extent summarizes many common views on memory as a scientific object today. In the neurosciences, memory has been defined as (1) the ability to encode, store, consolidate and retrieve information, (2) as a hypothetical store where information is kept, (3) as the information that is stored, but not in physical terms such as engrams or memory traces, (4) as the process that allows us to retrieve information from where it is stored, including the ability to do something that we have just learned, or (5) as our ability to consciously know that we remember things. Traditionally, two common orientations have been used to describe memory. One perspective proposes multiple memory systems, and the other focuses on mental processes in terms of dynamic patterns in neural activity or by synaptic functionality with regard to how we encode or retrieve memories. There is considerable overlap between the current understandings of these two perspectives.
**Declarative and nondeclarative memory**

Ryle (1949) identified two forms of long-term memory systems based on what he considered as “knowing what” and “knowing how”. Memories that consist of factual knowledge and personal events (i.e., memories that we encode, store, and later consciously recall) were labeled by Ryle as declarative memories. Memories that are unconscious to us (e.g., learning how to ride a bicycle) but that are necessary to deal with everyday living he labeled as nondeclarative memories. Today, declarative and nondeclarative memory is sometimes referred to as explicit and implicit memory. Of primary interest in this thesis is declarative rather than nondeclarative memory. Declarative memory has been further divided into two sub-forms or systems.

**Episodic and semantic memory**

Nielsen (1958) stated that there were two separate "tracks" in the brain for two different types of conscious memory, one for time and events that revolves around the person, and one for knowledge, often acquired through study. A similar two-part division came to be known as episodic and semantic memory (Tulving, 1972, 1983), concepts still in use today. The episodic memory, which is a rather fluid ability (i.e., less dependent of acquired knowledge), is assumed to hold memories that refer to a particular event or place and to our ability to mentally be able to travel backward and forward in time. Thus, episodic memory refers to memory of personally experienced events such as what we had for breakfast or what we did on vacation. Episodic memory is sometimes divided into subcomponents such as recall and recognition (Nyberg et al., 2003). Recall refers to our ability to recollect information from the past in the sense that we have a mental representation that makes it possible for us to talk about earlier events and processes. Recognition, on the other hand, refers to our ability to make a judgement that a repeated event corresponds to a past event (Saumier & Chertkow, 2002).

Semantic memory—which is a crystallized ability (i.e. dependent on acquired knowledge)—deals with facts, ideas, meanings, and concepts as well as an understanding of how parts of knowledge are related. Semantic memory is dependent on what knowledge a person has gained throughout life, for example, through education. It can, for instance, concern geographical and historical knowledge (Passer & Smith, 2007) but also includes linguistic skills and the understanding of letters and symbols. Semantic memory, just as episodic memory, is sometimes divided into subsystems. Nyberg et al. (2003), for example, proposed a distinction between semantic knowledge and semantic (word) fluency.

In summary, one can say that episodic memory enables us to move ourselves mentally to a particular event or place, both in the past and in the
future (autonoetic), whereas semantic memory is only conscious knowledge that might not be related to any past or future event or location (noetic) (Tulving, 1972, 1983).

**Episodic and semantic memory functions in normal aging**

Based on mean performance in several cognitive tasks, longitudinal data from the Betula study (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005) have indicated that episodic memory ability is relatively stable until the age of 60 to 65, after which a gradual age-related decline is observed. This is in contrast with cross-sectional data (e.g., Park, Lautenschlager, Hedden, Davison, & Smith, 2002) that have suggested that several cognitive abilities (e.g. free recall, cued recall) show an approximately linear decrease from early to late adulthood with an onset of decline as early as age 20 or 30. The magnitude of age-related memory differences and changes might, however, depend on whether recall or recognition is considered as the outcome measure (Spencer & Raz, 1995). More specifically, it has been argued that aging generally has a less pronounced negative effect on measures of recognition than on recall (e.g., Botwinick & Storandt, 1980; Craik, 1977) because recognition tasks require less processing resources (Craik & McDowd, 1997). An alternative explanation is that older adults generally use less strategic search methods for recall compared to younger individuals. It has also been suggested that the elderly, in general, recollect more integrative and interpretive information from an event, whereas younger people have a better ability to recollect more specific details of the to-be-recalled event (Zacks & Hasher, 2006). Apart from putative differences between subsystems of episodic memory, age-related decline in episodic memory appears to be a part of normal aging. Finding methods to enhance performance, however, or to at least postpone a decline in episodic memory abilities, is important because impairment in episodic memory functioning is also a common feature of dementia pathology (Cabeza, 2004). Thus, factors that strengthen episodic memory functioning should be identified.

Turning to semantic memory, Rönnlund et al., (2005) showed longitudinal increments in average performance levels from the age of 35 up to young-old age (age 65), after which a modest decline was observed such that the old-old adults (80 years or older) were still almost at a level of 35-year-olds. It has also been suggested that tasks that require fast retrieval of semantic information, such as rapid generation of words beginning with one particular letter (letter fluency), are more age sensitive than other semantic knowledge tasks (see Nyberg et al, 2003; Zacks & Hasher, 2006). However, it should be noted that such differences might be due to a slowing in the speed of information retrieval rather than to a loss of semantic representations. Deterioration in speed is relatively common at older age (Clay et al., 2009; Salthouse, 1996), and, thus, it possible that semantic
knowledge remains relatively stable over the life span, once speed is adjusted for.

**Working memory**

Working memory can be defined as a limited system that deals with temporary storage and manipulation of information (Baddeley, 2000). Working memory is highly useful in a variety of everyday situations such as reading, driving a car, remembering telephone numbers, etc. Working memory is assumed to underlie several complex mental processes and has historically been regarded as a system critical to our ability to plan and act in different situations (Miller, Galanter, & Pribram, 1960). Working memory is generally assumed to include both storage and processing components, and the latter can be seen as something that distinguishes working memory from short-term memory, which has been considered as a component that temporarily holds a limited amount of information (see Atkinson & Shiffrin, 1968). Although alternative interpretations of how we handle temporary and conscious information have been put forward throughout history, and concepts such as primary memory, focus of attention, or selective attention have been used (see Broadbent, 1958; Cowan, 2005; James, 1890; Unsworth & Engle, 2007), working memory is a commonly used term.

A classical model of working memory was introduced by Baddeley and Hitch in 1974 in which they considered working memory as a multicomponent system. A more refined model (Baddeley, 2000) includes one control system comprising the executive function and three slave systems comprising the phonological loop, the visuospatial sketchpad, and the episodic buffer. The executive function manages and manipulates our attention with the help of the slave systems and is considered to be a higher cognitive function because the slave systems are expected to operate under the executive function. Because the central executive function serves to regulate the flow of information within the working memory system, it is an important component in the control of our thoughts and actions. The slave systems can only maintain and manipulate a limited amount of information at a time. The phonological loop stores phonological information, and by using subvocal rehearsal it can help us hold information for a short time. The visuospatial sketchpad maintains and manipulates visual and spatial information, and the episodic buffer, also limited in its nature, serves as a multi-dimensional coding system. The episodic buffer is believed to integrate information from both the visuospatial sketchpad and the phonological loop, as well as information from the sense organs and the long-term memory, and to bind together information from the various components as multidimensional representations (chunks) that enable us to understand and make use of the information.
With regard to this thesis, a further description of working memory will be restricted to processing of visuospatial information because this is the only component of the memory systems that was measured in the three studies.

**Visuospatial ability**

Visuospatial ability refers to our ability to manipulate and handle visual and spatial information (Baddeley, 2000) and to be able to visually perceive and understand spatial relationships between objects (Lohman, 1988). It has, furthermore, been proposed that the visuospatial sketchpad can be divided into a visual cache and an inner scribe. The visual cache, a relatively passive component, refers to our ability to hold information about, for example, color and shape. The inner scribe is a rather active component that helps us deal with spatial and movement information (Mammarella, Pazzaglia & Cornoldi, 2008). However, the distinction between these components is not straightforward, and visuospatial tasks require both components to be active (Klauer & Zhao, 2004).

It should also be pointed out that in models of cognitive abilities based on factor-analytic approaches (for example, the hierarchical model by Carroll, 1993), visuospatial ability is considered as a separate ability factor (general visualization) that, together with other second-order cognitive factors, is subsumed by a general ability factor.

**Visuospatial ability in normal aging**

In old age there seems to be a pronounced age-related deterioration in the efficiency and speed of handling visuospatial material compared to, for example, verbal information. In addition, when cross-sectional data are considered, visuospatial ability seems to show a relatively early age of onset of decline (e.g., Kaufman, 1989; Park et al., 2002). In contrast, longitudinal data regarding spatial orientation suggest that visuospatial performance can be relatively stable until reaching 40 years (see Sands, Terry, & Meredith, 1989) or even up to age 55 (see Rönnlund & Nilsson, 2006a). The fact that an onset of decline in visuospatial ability is observed at higher ages might be due to the fact that spatial tasks are heavily dependent on right parietal lobe functioning (see Warrington, James & Maciejewski, 1986). With increased age, there seems to be a redistribution of activity to prefrontal regions when solving intellectual problems (Davis et al., 2008), and it has been suggested that this change in activation can be a part of compensatory processes that comes with aging.

**Differentiating dementia progress from normal aging**

Considering the consequences of dementia diseases, differentiating “abnormal” from “normal” cognitive aging as early as possible is crucial to
allow deployment of all available resources to postpone the onset of dementia. Some differences have been identified. A meta-analysis by Bäckman et al. (2005) revealed impairment across several cognitive functions, and these impairments were most pronounced in episodic memory, executive functioning, and perceptual speed prior to an AD diagnosis. Deficits were also observed in measures of attention and verbal and visuospatial abilities, although these impairments were less pronounced. The results of their analysis also indicated that individuals who developed AD experienced cognitive deficits several years before the clinical diagnosis. Results on the Mini-Mental State Examination (MMSE), an indicator of global cognitive functioning and a composite of different cognitive abilities, follow the same pattern. The subscales of the MMSE—orientation in time, orientation to place, and delayed recall—are the most significant in predicting AD three years before diagnoses. Thus, the ability to identify the risk of AD increases significantly when tasks are assessing multiple cognitive domains. Studies have also reported preclinical signs prior to other dementia diseases, such as impairment in memory (including subscales of MMSE) and fluency abilities prior to onset of vascular dementia (VaD) (e.g., Ingles, Wentzel, Fisk, & Rockwood, 2002; Jones, Jonsson Laukka, Small, Fratiglioni, & Bäckman, 2004) and in tasks related to frontal systems prior to frontotemporal dementia (Geschwind et al., 2001). Although quickness in thinking and remembering deteriorates in normal aging, it should be noted that it is still, compared to abnormal aging, possible to learn new information. In addition, even if it might become more difficult to switch between and handle multiple tasks, such increased task demands are often manageable. Further, it is still possible to use strategies, and make behavioral changes, to compensate for cognitive changes.

The complexity of differentiating dementia progress from normal aging must, however, be highlighted. As previously described, a decline in some abilities (e.g., episodic memory and visuospatial ability) is usually a part of normal aging. In addition, age-related changes in thinking and remembering and dementia pathology can often occur simultaneously and can be very subtle (Insel & Badger, 2002). Thus it is sometimes difficult to determine if changes, at least in early stages, are pathological or not. In addition, neural changes often exhibit a slow progress prior to dementia (Bäckman et al, 2005), and it is possible that a certain threshold must be reached before cognitive impairment is manifest in test performance. Furthermore, impairment in memory functioning in old age is not necessarily indicative of dementia; it can also be a sign of depression or delirium, and this makes diagnosis difficult (Insel & Badger, 2002).

In conclusion, although there are features differentiating normal aging from dementia progress, increased knowledge of what more precisely
characterizes those who have, or have not, entered the transitional state is needed.

**Dementia disorders**

The most common cause of accelerated cognitive decline, at least among the older part of the population, is dementia, and the incidence of dementia increases after the age of 65 (Wimo et al., 1997). Dementia is a general term that refers to many different diseases that cause long-term reductions in the ability to think and reason normally, changes that, in turn, lower everyday functioning and gradually make independent living impossible. Dementia is characterized by a progressive decline in several cognitive abilities, including memory, learning ability, thinking, language skills, judgment, and perception. Dementia can additionally result in severe behavioral and emotional disorders (Duguè et al., 2003; Salomon & Budson, 2011). Dementia diseases are chronic and progressive disorders that affect large parts or regions of the brain, and these changes cause psychopathological symptoms. The cognitive deficits and behavioral changes depend on the localization of the disease in the brain (Kurz & Lautenschlager, 2010). Thus, dementia is not considered to be a disease in itself, but rather as a syndrome and a term reflecting multiple cognitive deficits (see DSM IV; American Psychiatric Association, 2000). In the latest version of DSM (see DSM V; American Psychiatric Association, 2013) the term dementia has been replaced by major neurocognitive disorder and mild neurocognitive disorder. Despite this recent change in terminology, however, the term dementia is still widely used, for instance, by the Alzheimer’s Association. The term dementia was, therefore, used in this thesis.

**All-cause dementia**

Considering dementia, regardless of form (all-cause dementia) is motivated in studies where one wants to examine how different factors are related to dementia. Although there is support for distinguishing among sub-types of dementia, it has recently been shown that vascular symptoms are relatively common even among those who develop neurodegenerative diseases (Grinberg & Heinsen, 2010; Korczyn & Vakhapova, 2007). The risk for vascular changes increases as age increases, and thus an interaction with neurodegenerative diseases is more common. Therefore, mixed causes of dementia might be more common than previously thought (Langa, Foster, & Larson, 2004). In fact, there are those who argue that mixed causes extremely common and that most cases of dementia are based on mixed causes (Korczyn, 2002a; Strozyk et al., 2010; Schneider, Arvanitakis, Bang & Bennett, 2007). According to Grinberg & Heinsen (2010) mixed brain pathologies might be behind as many as 73% of all cases of AD and VaD. Based on these findings, it may be difficult to judge which of the two diseases
are most influential in cases of cognitive impairment. The overlap between dementia forms could possibly be seen in the light of a continuum, with AD (or similar) pathology at one end and VaD at the other (Kalaria, 2002), and the main cause of incident dementia could then be determined depending on the position on this continuum.

It should be noted that there is an overlap in terms of risk factors for different types of dementia. Apolipoprotein (APOE) ε4, for example, is not only a risk factor for AD (Farrer et al., 1997; Smith, 2002), but it has also been associated with vascular diseases (e.g., Frisoni et al., 1994; Stengard et al., 1995; Treves et al., 1996). Other factors such as age, poor education, coronary artery disease, hypertension, and smoking have been associated with increased risk of both AD and VaD (Korczyn, Vakhapova, & Grinberg, 2012). Thus, given that there might be an overlap between types of dementia, and that some risk factors are shared (some of which possibly can be explained by the overlap), it might be important to investigate dementia as a general outcome (all-cause dementia) in analyses where one wants to examine how different factors are related to dementia. For this study, irreversible and progressive dementias included in analyses of all-cause dementia are forms AD, VaD, Lewy body dementia, frontal lobe dementia, Parkinson’s dementia, and unspecified dementia.

**Alzheimer’s disease**

AD is considered to be a late-life disease (Dugué et al., 2003) and is often considered to be the most common cause of dementia (Bird, 2008; Corder et al., 1993) accounting for about 60–70% of all dementia cases (Fratiglioni et al., 2007). It is a neurodegenerative disease characterized by a progressive loss of intellectual and cognitive abilities. For example, episodic memory is often impaired in AD (Cabeza, 2004). There are some known physiological factors regarding how AD affects the brain, including loss of brain neurons and synapses (Wenk, 2003), brain atrophy, reductions in brain activity, reduced blood flow in certain brain areas, reduced glucose metabolism, higher levels of amyloid-beta plaques and neurofibrillary tangles, and increased white-matter hyperintensities (Bäckman, Jones, Berger, Laukka, & Small, 2005). In addition to physiological aspects, AD is often accompanied by depressive symptoms, anxiety, irritability, aggression, apathy, delusions, and sleep and eating disturbance (Mirakhur, Craig, Hart, McIlroy, & Passmore, 2004). AD will, in the end, impair the ability to manage everyday life. Although the severity and the speed of progression of AD differ substantially between individuals, the clinical course for the disease is well established (McDowell, 2001). To obtain a clinical diagnosis of AD according to the DSM-IV (4th ed., American Psychiatric Association, 2000), it is required that impairments are present in more than one cognitive function.
During the early stages of the disease, patients often suffer from modest forms of memory loss and tend to have difficulties with use of language and attention. As the disease progresses, cognitive abilities are impaired further, and the individual will eventually become dependent on help to handle what were previously considered to be simple everyday tasks. Unfortunately the person might additionally face significant personality and behavioral changes, and it is not unusual that a person with AD wanders around aimlessly, sometimes resulting in leaving their home and being unable to return. When AD is exhibited in its worst form, the person is no longer able to speak normally and can no longer understand what others say, and the AD patient requires constant care to cope with basic everyday tasks such as eating, moving, toilet visits, and washing (Sloane et al., 2002). Today there is no cure for AD. However, because treatment might slow its progression, early diagnosis is important (Dugué et al., 2003).

**Vascular dementia**

VaD is considered the second most common form of dementia, and the risk of VaD increases significantly with increased age (Middleton, Grinberg, Miller, Kawas, & Yaffe, 2011). Recent studies indicate that the prevalence of VaD might have been underestimated and that cognitive impairments related to VaD are more common than previously thought (Grinberg & Heinsen, 2010; Korczyn & Vakhapova, 2007; Roman, 2002). It has also been shown that cardiovascular pathology can often interact with other neurodegenerative diseases (Korczyn 2002a, 2002b). VaD can be caused by a stroke or damage to multiple blood vessels in the brain. Although some damage to blood vessels and nerve fibers in the brain is a relatively normal part of aging, such damage can cause different forms of brain tissue lesions (Kalaria, 2002). VaD can also be caused by hemorrhage, infarction, hippocampal sclerosis, cortical laminar necrosis, and white-matter lesions (Grinberg & Thal, 2010).

There are some characteristics of VaD, including impaired attention (working memory and executive functioning), worsening memory of contextual information, difficulties with planning and problem solving, impaired motor and information processing, and worsening language and writing skills. Disorientation and behavioral and emotional disturbances are also relatively common (Sachdev et al., 2004; Nordlund et al., 2007). Although they have difficulties with recall, VaD patients often have better recall abilities compared to AD patients (Korczyn, Vakhapova & Grinberg, 2012). VaD also manifests as deterioration of memory capacities similar to that of normal aging, although with greater impairment (Cabeza, 2004). The cognitive reductions might initially be observed as mild changes and then progressively get worse. The gradual impairment can, in some cases, be slower than in AD (Bruandet et al., 2009). However, the cognitive changes
depend on the extent of the injury and the parts of the brain that are affected. Brain lesions are often heterogeneous, causing a range of cognitive deficits, and abilities can deteriorate cumulatively based on ongoing lesions (Korcyn et al., 2012). Today, the term ‘vascular cognitive impairment’ is commonly used to describe the severity of VaD progression. As for AD, VaD can vary from mild to severe, and some consider such terminology a useful tool to describe differences among patients (Roman et al., 2004). Although changes in lifestyle behaviors can possibly mitigate or decrease some risk factors associated with VaD, there is no cure for VaD.

**Other dementias**

Other dementias include frontal lobe dementia (FTD), Lewy body dementia (DLB), Parkinson's dementia (PDD), and unspecified dementia (NUD). FTD is an age-related form of dementia, although it often starts earlier than other dementia diseases, sometimes between 45 and 65 years of age (Snowden, Neary & Mann, 2002). The term is used to describe dementias producing focal lobar atrophy in the frontal lobe and/or temporal lobes (Brun et al., 1994; Miller et al., 1997) and can have a long clinical course (McKhann et al., 2001; Seelaar, Rohrer, Pijnenburg, Fox & van Swieten, 2011). Differentiating FTD from other dementia diseases, for example AD, is dependent on the brain region that is affected (Hultch & MacDonald, 2004). For example, compared to AD, in which episodic memory is impaired due to reductions in hippocampal regions, FTD patients often show difficulties in tasks believed to draw heavily on frontal lobe functioning such as working memory and executive functioning (Cabeza, 2004; Seelaar et al., 2011), and deficits in other memory capacities are not prominent features of FTD (Brun et al., 1994; Rosen, Hartikainen & Jagust, 2002). FTD patients often suffer from problems with both expressive and receptive language and with changes in personality and behavior expressed as disinhibition, withdrawal, and apathy (McKhann et al., 2001; Rosen et al., 2002), although these symptoms are common in other dementias as well (Braaten, Parsons, Mccue, Sellers, & Burns, 2005).

Regarding PDD and DLB, the mental state can vary considerably in the patient from one moment to the next (Emre et al., 2007; McKeith et al., 2005). Both PDD and DLB are neurodegenerative conditions having many biological factors in common. Some researchers have used the umbrella term “Lewy body dementias” to refer to both PDD and DLB because in both conditions protein accumulations—so-called “Lewy bodies”—are often found in the brain (Tröster, 2008). PDD is characterized by a lack of dopamine (Cabeza, 2004), but this deficiency is also present in DLB. DLB is manifested as a significant loss of the neurotransmitter acetylcholine (Sarter & Bruno, 1998; Shiozaki et al., 1999). DLB is often accompanied with AD neuropathology (Marui, Iseki, Kato, Akatsu, & Kosaka, 2004), and many
Lewy body disorders include the presence of plaques and tangles similar to those seen in AD (Kaufer and Tröster 2008). Both DLB and PDD often result in difficulties with handling three-dimensional information, and visual hallucinations are relatively common (Aarsland, Andersen, Larsen & Lolk, 2003; Weintraub & Hurtig, 2007). Although attention abilities often become affected, memory impairment is not always persistent in the early stages of DLB and PDD. It is not uncommon for people with DLB or PDD to fall and suffer fractures. Blood pressure instability, sleeping problems, and depression are also common among these patients. Although there is a significant overlap, some features often associated with DLB are cognitive changes that interfere with social and occupational function and unexplained loss of consciousness, whereas PDD is often accompanied by impaired executive functioning, problems with word-finding, impaired memory for recall, apathy, and changes in mood and personality (McKeith et al., 2005; Emre et al., 2007).

Additional factors associated with cognitive functioning and risk of dementia

The main purpose of this chapter is to describe how different factors, in addition to leisure activities and social activities, are related to cognitive function and risk of dementia. A short empirical background is presented for each of these factors in order to justify the choice to include these in the three studies that make up this thesis. The background information might not be of special interest only when interpreting the results in relation to leisure activity and social relationships. Although many of these factors can be related to each other, these relationships will only be briefly discussed.

Demographic factors

Aging is, undoubtedly, a major risk factor for cognitive decline and dementia. Even though there are many psychosocial factors that can influence cognitive aging, it is unavoidable that the biological aging process of the brain has a large impact (Bäckman & Nyberg, 2010). Although trajectories for different cognitive abilities seem to differ between different memory abilities over time on a general level, a decline in several cognitive abilities is still a common part of the aging process. In addition, the aging process is by nature accompanied by many changes both in brain structure and brain activity, changes that can ultimately have negative effects on cognitive function (Raz et al., 2010). Changes in brain activity that come with aging can also reflect brain plasticity that serves to preserve cognitive functions (Lövdén, 2010).

A number of studies have also investigated gender differences in relation to dementia risk. The results have been mixed, and some studies suggest that women are at higher risk of all-cause dementia than men (e.g.,
Brayne et al., 1995) whereas others find no sex difference (Bachman et al., 1993). It has also been reported that women are at higher risk of AD (Gao, Hendrie, Hall, & Hui, 1998), but with no gender difference in risk of VaD (Andersen et al., 1999). In addition, differences in certain cognitive abilities have been reported. It is generally assumed that women perform better on episodic memory tasks (e.g., Herlitz et al., 1997; Lewin & Herlitz, 2002) and on measures of verbal ability (e.g., Hooren, Valentijn, Bosma, Ponds, van Boxtel, & Jolles, 2007; Hyde & Linn, 1988), while men tend to perform slightly better on tests measuring visuospatial ability such as mental rotation tasks (e.g., Colom, García, Juan-Espinosa, & Abad, 2002; Rönnlund & Nilsson, 2006a). In tasks that measure both visuospatial and verbal skills (e.g., pointing out an object's previous location), however, women show a tendency to perform better than men, probably because women use their verbal ability to remember the location of the object (Herlitz, Lovén, Thilers, & Rehnman, 2010). It has also been suggested that among the oldest old (85+ years), women perform better on tasks measuring memory (word-list) and cognitive speed (Van Exel et al., 2001).

Gender differences also appear to be stable over time. For example, de Frias, Nilsson, and Herlitz (2006) found that over a 10-year period women performed better on tasks measuring semantic fluency, episodic recall, and recognition, whereas men performed better on a measure of visuospatial ability (WAIS-R Block Design test), and these differences were stable over time. In a similar vein, Gerstorf et al., (2006) reported a parallel longitudinal decline in men and women in old age (70–100 years), with women showing higher overall levels of performance across the cognitive domains (episodic memory, verbal fluency, verbal knowledge, and perceptual speed). The authors concluded, however, that gender differences could be masked by differences in sample attrition.

Educational level is often regarded to be one of the major components that contributes to the cognitive reserve (Stern, 2002), and many studies have found that educational level is associated with reduced risk of cognitive impairment and dementia (e.g., Brayne & Calloway, 1990; De Ronchi, Fratiglioni, Rucci, Paternico, Graziani, & Dalmonte, 1998; Evans et al., 1997; Gatz, Svedberg, Pedersens, Mortimer, Berg, & Johansson, 2001; Katzman, 1993; Mortel, Meyer, Herod, & Thornby, 1995; Stern, Gurland, Tattemichi, Tang, Wilder, & Mayeux, 1994). A meta-analysis (Valenzuela & Sachdev, 2006) of cohort studies suggests that higher levels of education, together with other beneficial lifestyle factors, reduces the risk of future dementia. In their literature review, Sharp & Gatz (2011) reported, however, that even if lower education has been related to higher risk of dementia, many studies do not support this assumption, and associations found between education and dementia may depend on the specific study populations used. Furthermore, the relationship with dementia seemed to be stronger when years of
education reflected cognitive capacity. The authors suggested, therefore, that future studies would benefit from using a lifespan perspective when including education into their models. Studies have also found that educational attainment attenuates cognitive decline among non-demented elderly (e.g., Albert et al., 1995; Butler, Ashford, & Snowdon, 1996; Evans et al., 1993; Farmer, Kittner, Rae, Bartko, & Regier, 1995; Lyketsos, Chen & Anthony, 1999), although more recent studies have indicated a relationship to levels of cognitive functioning but not to rate of cognitive decline (Christensen, Hofer, MacKinnon, Korten, Jorm, & Henderson, 2001; Glymour, Weuve, Berkman, Kawachi, & Robins, 2005; Tucker-Drob, Johnson, & Jones, 2009; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008; Wilson, Hebert, Scher, Barnes, Mendes de Leon, & Evans, 2009). This pattern seems to hold for several cognitive abilities such as processing speed, working memory, verbal fluency, and verbal episodic memory (Zahodne et al., 2011).

Finally, marital status is a factor that has been associated with a number of health aspects. Married people, compared to those who are divorced, single, widowers, or widowed, tend to have lower levels of mortality (Ikeda, Iso, Toyoshima, Fujino, Mizoue, & Yoshimura, 2007; Kiecolt-Glaser & Newton, 2001), higher self-reported health (Mercenes & Sheiham), better cardiovascular functioning (Carels, Sherwood, & Blumenthal, 1998), and lower levels of depression (Kiecolt-Glaser & Newton, 2001), factors that, in turn, might affect risk of cognitive decline and dementia (e.g., Anstey & Christensen, 2000; Jorm, 2001; Ownby et al., 2006). Living in a partnership has also been proposed to increase cognitive stimulation (van Gelder et al., 2006), and could, therefore, contribute directly to the cognitive reserve (Scarmeas & Stern, 2003; Stern, 2002). Several studies have shown that not living with a partner is associated with cognitive decline (Van Gelder, Tijhuis, Kalmijn, Giampaoli, Nissinen, & Krombou, 2006) and dementia (Bickel & Cooper, 1994; Håkansson et al., 2009; Helmer et al., 1999; Sundström, Westerlund, Mousavi-Nasab, Adolfsson, & Nilsson, 2014). In addition, living in a partnership might have positive effects on specific forms of memory. For example, Mousavi-Nasab, Kormi-Nouri, Sundström, and Nilsson (2012) found, by following participants over a period of five years, that married people have better cognitive ability in terms of episodic memory. Furthermore, the rate of cognitive decline was greater in those who were single (not living in a partnership), an outcome that was attributable to both middle-aged (35–60 years) and older (65–85 years) individuals.

**Health**

As previously noted, many illnesses and poor general health that come with higher age reduce the possibilities of engagement in activities (Bukov, Maas,
Lampert, 2002), a limitation, that in turn, can have a negative influence on cognitive functioning. Still, although it has been difficult to relate several objective (e.g., glucose level, hemoglobin value) and subjective (e.g., feeling healthy or not) measures of health directly to cognitive functioning (see Nilsson et al., 1997), there still are a number of health factors that have been associated with cognitive functioning. Cardiovascular risk factors such as heart attack/cardiovascular problems, diabetes, high blood pressure (hypertension), and stroke have all been negatively associated with cognitive functioning (see Anstey & Christensen, 2000; Bäckman, Jones, Small, Aguero-Torres, & Fratiglioni, 2003; Launer et al., 2000; Qiu et al., 2003), and it should be noted that bad health, in general terms, seems to affect fluid abilities more than crystallized abilities (Anstey & Christensen, 2000). In addition, having several different diseases at the same time might have even more negative impacts on cognitive ability and risk of dementia, and because aging is often accompanied by multiple diseases (Cauley, Dorman, & Ganguli, 1996), the risk of cognitive deficits can increase due to this situation. Even if it is assumed that the biological aging process itself has the largest influence on variation in cognitive ability, while also taking into account diseases that become more common with increasing age (Wahlin, 2004), it might still be that the age factor is overestimated. By overestimating the effect of age in general, it is plausible that various health aspects that might affect cognition are overlooked (Spiro & Brady, 1998).

Another health-related factor is being overweight or obese, and it is well known that being overweight can have several adverse health outcomes. Although few in number, there are studies that suggest that increased body weight (body mass index (BMI) > 30) is associated with worsening cognitive function (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005) and has a negative influence on executive and visuomotor abilities (Wolf, Beiser, Elias, Au, Vasan, & Seshadri, 2007). Obesity is also believed to increase the risk of dementia. It has, for example, been found that people who are obese in middle-age are at higher risk of future dementia (Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005) and that this might be an indicator of future dementia as much as three decades before onset (Whitmer, Gustafson, Barrett-Connor, Haan, Gunderson, & Yaffe, 2008). It has also been suggested that obesity in middle age (BMI > 30) is a risk factor not only for dementia in general, but also for AD (Kivipelto et al., 2005). A systematic review and meta-analysis conducted by Beydoun, Beydoun, and Wang (2008) provided overall support for an association of obesity with all-cause dementia and AD. Still, the associations were moderate and the authors concluded that more studies are needed.

Despite these patterns, there is a paradox regarding the relationship between obesity and dementia. Fitzpatrick et al. (2009) found, in agreement
with the aforementioned studies, that midlife obesity could be related to future dementia. However, the authors also found that in old age the relationship was reversed. More specifically, older individuals classified as obese were found to have a reduced risk of dementia, while underweight people were at a higher dementia risk. This reversed relationship in old age might reflect the fact that dementia is often characterized by weight loss. Other studies also provide support for reduced BMI being related to increased risk, at least for AD (Buchman, Wilson, Bienias, Shah, Evans, & Bennett, 2005; Johnson, Wilkins, & Morris, 2006).

Stress is another health aspect that can be associated with cognitive functioning. Chronic stress can contribute to the development of diseases by causing increased vulnerability in individuals (Marin et al., 2011). Prolonged stress might, for example, increase the risk of depression (Hammen, 2005) and cardiovascular diseases (Cohen, Janicki-Deverts, & Miller, 2007), which in turn might have adverse effects on cognitive performance. High levels of stress, however, can also have a direct link with impaired memory function. Cognitive abilities can be negatively affected by long-lasting stress (Bremner et al., 1993; Gil, Calev, Greenberg, Kugelmass, & Lerer, 1990; Golier et al., 2002), stressful life events (e.g., Sands, 1981–1982; Vondras, et al., 2005), stress-related exhaustion (Öhman, Nordin, Bergdahl, Slunga Birgander, & Stigsdotter Neely, 2007; Sandström, Nyström, Lundberg, Olsson, & Nyberg, 2005; Van der Linden, Keijzers, Eling, & Van Schaijk, 2005), and high levels of cortisol, a biomarker of stress (e.g., Li et al., 2006; Lupien et al., 1998), although consistent results are not observed across the board (e.g., Comijs et al., 2010; Csernansky et al., 2006; Kohler et al., 2010). Studies have also shown that the hippocampus, which is important for memory functioning, is adversely affected by prolonged stress (Bannerman et al., 2004; Gould & Tanapat, 1999; McEwen, 2000; Sapolsky, 2000) and that stress can be related with reduced neurogenesis in the hippocampus (Gould & Tanapat, 1999; Sousa, Lukoyanov, Madeira, Almeida, & Paula-Barbosa, 2000).

Johansson et al. (2010) investigated whether midlife psychological stress was related to later life dementia (AD, VaD, and others) among women. Stress was measured at three occasions in midlife with 6-year intervals. The results revealed that the risk of future dementia significantly increased with the number of stressors reported. Sundström, Rönnlund, Adolfsson, and Nilsson (2014), however, found no association between negative or positive life events and risk of dementia.

Finally, another factor that has been negatively related to cognitive functioning is depression. Even though it is associated with decreased physical, social, and mental activity (e.g., Wilson, Barnes, & Bennett, 2007; Elias & Wagster, 2007), it is a preclinical symptom of dementia, and it is a common feature among dementia patients (Ballard et al., 2000; Park et al., 2007), a number of studies argue that depression also increases risk of all-
cause dementia and AD (for reviews and meta-analyses see Diniz, Butters, Albert, Dew, & Reynolds, 2013; Gao et al., 2013; Jorm, 2001; Ownby et al., 2006). It should be noted, however, that lack of associations have also been reported (e.g., Becker et al., 2009; Lindsay et al., 2002).

Different outcomes from studies can, at least partly, be explained by differences in the frequency and severity of depression (Byers & Yaffe, 2011). Also, even if many studies have focused on late-life depression (>60 years of age), it seems that depressive symptoms earlier in life also constitute a risk factor. A recent longitudinal study found that depressive symptoms in midlife as well as in late-life were associated with dementia (Barnes, Yaffe, Byers, McCormick, Schaefer, & Whitmer, 2012). They also found that recurrent depression seems to be associated with higher risk of VaD, whereas depression that begins later in life can be part of the AD prodrome.

Sachs-Ericsson et al. (2005) found that depressive symptoms predicted cognitive decline over a follow-up of three years among elderly persons who had no cognitive impairment at baseline. Furthermore, Sawyer, Corsentino, Sachs-Ericsson, and Steffens (2012) found that depression was associated with a decrease in right hippocampal volume, and, therefore, they suggested that there might be a causal relationship between depression and cognitive decline. A number of other studies have found an association between severe depression and decreased size of the hippocampus (Sheline, Sanghavi, Mintun, & Gado, 1999; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; for exceptions, see: Ashtari et al., 1999; Rusch, Abercrombie, Oakes, Schaefer, & Davidson, 2001).

**Lifestyle**

Smoking is undoubtedly negatively related to many health outcomes. In recent years, interest has increased in terms of the relationship of smoking to cognitive factors. It has been reported that smoking can be associated with decreased risk of dementia (Almeida, Hulse, Lawrence, & Flicker, 2002), but later meta-analyses, based on longitudinal studies, have found that smoking overall is related to increased risk of cognitive decline, all-cause dementia, VaD, and AD, although results are mixed (Anstey, von Sanden, Salim, & O’Kearney, 2007; Cataldo, Prochaska, Glantz, 2010; Peters, Poulter, Warner, Beckett, Burch, & Bulpitt, 2008). A history of heavy smoking (≥ 1 pack per day) can be related to a 2–3 year earlier onset of AD (Harwood et al., 2009). It should be noted, however, that nicotine has been suggested to have positive short-term effects on cognition, with improved attention, and has also been positively associated with short-term and long-term memory performance (Murray & Abeles, 2002).

Another common lifestyle feature is alcohol consumption. Although it has been found that long term and extensive alcohol consumption might impair cognitive processing, and also result in so called alcohol-related
dementia (Mukamal et al., 2006; Oslin, Atkinson, Smith, & Hendrie, 1998), meta-analyses of 15 prospective studies (with follow-ups of 2–8 years) by Anstey, Mack, and Cherbuin (2009) investigating the relationships between alcohol consumption and dementia and cognitive decline revealed that relative risks were lower for all-cause dementia (and also for AD and VaD separately) for light to moderate drinkers compared with non-drinkers. Also, when classified more generally as drinkers versus non-drinkers, alcohol consumption was associated with reduced risk for dementia and AD. Remarkably, heavy drinking was not associated with increased risk. A systematic review with meta-analyses on longitudinal studies (Peters, Peters, Warner, Beckett, Bulpitt, 2008) exclusively among the elderly (≥65 years) confirmed that small amounts of alcohol can actually be protective against all-cause dementia and AD, although associations were not significant for VaD or cognitive decline.

A recent study by Sabia et al. (2014) investigated the association between midlife (mean = 56 years) alcohol consumption and later risk of cognitive decline over a follow-up of 10 years. The results indicated that among men, excessive alcohol consumption was associated with more rapid cognitive decline in all measures of cognition (global cognition, executive functioning, and memory) compared with low or moderate consumption. Among women, those who abstained from alcohol showed faster decline than light or moderate drinkers, both in global cognition and in measures of executive functioning. Although the results were different for men and women, light to moderate alcohol consumption was not associated with risk of cognitive decline, and this was similar to the results of studies on the elderly.

Physical activity, another lifestyle factor, has been suggested to have cognitive and neural benefits (Churchill et al., 2002), and several studies have suggested that low physical activity increases the risk of cognitive impairment and dementia (e.g., Barnes, Blackwell, Stone, Goldman, Hillier & Yaffe, 2008; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Weuve, Kang, Manson, Breteler, Frog Ware & Stein, 2004; Yoshitake et al., 1995). It has, for example, been demonstrated that daily walking decreases the risk of cognitive decline among elderly women (Barnes et al., 2008; Weuve et al., 2004), and combining different forms of exercise appears to provide a larger effect on cognition among the elderly than simply engaging in unilateral training (Colcombe & Kramer, 2003).

It has also been suggested that exercise in midlife is associated with reduced odds of dementia later in life (Rovio et al., 2005; Andel, Crowe, Pedersen, Fratiglioni, Johansson, & Gatz, 2008). However, it should be noted that there are studies finding no relationship between physical activities and cognitive impairment (e.g., Wang et al., 2006) or dementia (e.g., Verghese et al., 2003). One reason for different outcomes might be due
to the lack of studies that have a sufficient number of participants. In addition, data are often based on different measures of subjective estimation of activity, rather than having objective measures, and thus the results are not sufficiently reliable (McAuley, Kramer & Colcombe 2003). Meta-analysis based on nearly 134 studies examining either acute or long-term exercise effects on cognition suggests that all together there is a small but positive impact of exercise and fitness on cognitive performance. Physically fit people seem to have a better ability to perform rapidly and more accurately on a number of tasks measuring perception and cognition than the physically unfit. Furthermore, exercise as a constant action to produce fitness, and/or adopted by an individual for a long period of time, seems to have an even larger impact on cognition (Etnier, Salazar, Landers, Petruzzello, Han & Nowell, 1997).

**Genetics**

The study of genetics is a growing frontier in cognitive aging, and it is clear that changes in cognitive functioning that come with aging can be influenced by both genetic and environmental factors (Gatz, et al., 2006). One factor associated with cognitive functioning is the Apolipoprotein E (APOE) gene (Corder et al., 1993), a gene that also has been related to health and longevity (Smith, 2002). APOE is a protein that, among other things, is involved in cholesterol transport and the processes of neuronal repair (Mahley, 1988; Rubinsztein, 1995). The gene coding for APOE is positioned on chromosome 19, and every individual holds two alleles, one from each parent. There are three types of alleles— \( \varepsilon_2 \), \( \varepsilon_3 \), and \( \varepsilon_4 \)—which make six combinations possible for each individual. The frequency of allele distribution differs among ethnic populations, with the \( \varepsilon_3 \) allele most common in the general Swedish population (Eggertsen, Tegelman, Ericsson, Angelin & Berglund, 1993).

Research suggests that if you are a carrier of the \( \varepsilon_4 \) allele you have an increased risk of faster cognitive decline (Corder et al., 1993; Nilsson et al., 2006) and increased risk of AD (Smith, 2002). A meta-analysis (Farrer et al., 1997) showed that among carriers of one APOE-\( \varepsilon_4 \) allele, the risk of developing AD increased 3 to 4 times compared to a non-carrier, and among those with two alleles the risk was 10 to 12 times higher. It has been suggested, however, that with increased age the APOE-\( \varepsilon_4 \) allele becomes less efficient in predicting the risk for developing AD (Smith, 2002), although it is still a potential risk factor later in life, particularly in homozygote carriers of the \( \varepsilon_4 \) allele. It should also be noted that the \( \varepsilon_4 \) allele has been associated with increased risk of other dementia diseases such as VaD (see Frisoni et al., 1994; Stengard et al., 1995; Treves et al., 1996). In contrast to the risk associated with APOE-\( \varepsilon_4 \), APOE-\( \varepsilon_2 \) has been suggested to be protective (Corder et al., 1994).
Research has also revealed that ε4-carriers, both middle-aged and elderly, although still cognitively healthy, perform worse on several cognitive tasks than non-carriers (e.g., Berr et al., 1996; De Blasi et al., 2009; Greenwood, Lambert, Sunderland, & Parasuraman, 2005; Helkala et al., 1995; Packard et al., 2007; Zehnder et al., 2009). Meta-analyses (Wisdom, Callahan, & Hawkins, 2011; Small, Rosnick, Fratiglioni, & Backman, 2004) confirm this pattern and demonstrate more pronounced differences on measures of perceptual speed, executive functioning, and global cognition. However, not all studies report an association between cognitive ability and the ε4 genotype (e.g., Bathum, Christiansen, Jeune, Vaupel, McGue, & Christensen, 2006; Chen et al., 2002; Garcia et al., 2008; Kim et al., 2002; Marquis et al., 2002; Salo et al., 2001).

The empirical studies

Main objectives
The overarching aim of this thesis was to longitudinally investigate the influence of social relationships and leisure activity on the risk of future dementia and age-related cognitive decline. The empirical studies conducted as part of this thesis were motivated by the cognitive reserve hypothesis, which assumes that mental stimulation is beneficial for cognitive functioning and might postpone the age of onset of cognitive decline and dementia.

Specific aims:

Study I:

To investigate the association between participation in various leisure activities in old age (≥65 years) and risk of incident all-cause dementia.

Study II:

To investigate the association between various aspects of social relationships in old age (≥65 years) and risk of incident all-cause dementia and AD.

Study III:

To investigate the association between social network size and cognitive ability in a middle-aged (40–60 years) sample.
Methods

The Betula Prospective Cohort Study
All three studies were based on data that emanated from the Betula Prospective Cohort Study (Nilsson et al., 1997, 2004). The Betula study is a longitudinal study on memory, aging, and health that started in Umeå, Sweden, in 1988. The aims of the study were to investigate how health and memory develop in adulthood and old age, to identify preclinical signs of dementia, and to assess premorbid memory function. Participants were selected from the population registry of Umeå using stratified (age, gender) random sampling with a narrow-age cohort design (5 years between each age cohort) and with a gender distribution representative of that in the Umeå community. Inclusion in the study required a non-demented status at time of entry, Swedish as a native language, and absence of severe visual or auditory handicaps.

Since 1998, data have been collected on six test occasions (1988-1990, 1993-1995, 1998-2000, 2003-2005, 2008-2010, and 2013-2014). At each occasion, participants were interviewed, tested cognitively, and examined medically. Participants were invited to two sessions, about one week apart. The first focused on a health assessment, and the second focused on an extensive examination of memory. The health examination was performed by a nurse, and testing of memory functions was performed by a trained research assistant. In addition to measurements of cognition and health (including information about life events, social situation, lifestyle, etc.), all participants were followed over time and followed-up with regard to dementia status by a clinical and research geriatric psychiatrist, and these follow-ups currently cover the period from 1988 to 2010.

The design of the Betula study, including the age range for each sample at inclusion, is presented in Table 1. The first sample (S1), assessed in 1998, included 1000 participants with 100 individuals in each age cohort (35 years, 40 years, 45 years, etc.). New samples have been included in the study, and in most cases the goal was to recruit 100 participants for each age cohort. Two new samples were included at test wave 2 (1993-95). Participants of S2 were as old as S1 was at test wave 1, whereas S3 were the same age as S1. So far about 4,500 individuals have participated in the Betula study.
Table 1. The design of the Betula Study. A stratified random sampling is used (age, sex) that corresponds to the distribution in Umeå.

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*Age range at inclusion

The Västerbotten Intervention Programme

Study III includes, in addition to data from the Betula study, information collected as part of the Västerbotten Intervention Programme (VIP) (Norberg et al., 2010). The VIP is an ongoing population-based intervention that started in 1985 in Norsjö, Sweden. The main purpose of the VIP is to reduce morbidity and mortality caused by cardiovascular diseases and diabetes, because in Sweden, especially in the county of Västerbotten in the north of Sweden, the number of mortality cases caused by cardiovascular diseases increased steadily during the 20th century. The VIP was subsequently implemented across Västerbotten, which also includes Umeå municipality. Since 1995, all inhabitants of Västerbotten that are 40, 50, and 60 years old are invited to voluntarily participate in the study to get a risk factor screening and to get individual counseling about healthy lifestyle habits. About 6,500–7,000 examinations take place each year, and the VIP includes data for almost 90,000 participants. Up to the year 2010, nearly 27,000 subjects had participated twice (Norberg et al., 2010).

The VIP is implemented in primary health care routines, and the assessment is carried out in a single session at the participant’s health center and includes a medical examination and a questionnaire including information about health, lifestyle, social situation, etc. The medical examination is performed by a nurse, and for each participant a health profile is created that is discussed with the nurse. The purpose of this is to encourage behavior that facilitates health, for instance, by changes in lifestyle habits that decreases the risk of heart disease, diabetes, stroke, etc.

The Linnaeus Database

Information from the Betula project and the VIP is linked within the Linnaeus database (Malmberg, Nilsson, & Weinehall, 2010). The database is
an anonymized longitudinal database that was established in 2009, and it is
designed to provide the opportunity for interdisciplinary research. The
database has been developed at the Centre for Population Studies at Umeå
University and includes information from several sources of Swedish register
data. In addition to data from the Betula study and the VIP, the Linnaeus
database contains information from Statistics Sweden and the National
Board for Health and Welfare, databases that, for example, provide
information about causes of death, hospitalization, and socio-economic
conditions. The database is designed for both cross-sectional and
longitudinal studies and provides the opportunity to examine relationships
between health status, cognitive function, lifestyle, various health indicators,
socioeconomic conditions, population dynamics, etc. Data from Betula are
available in the database up to T4 (2003-2005), and most of the cognitive
data are included. Data regarding genetics and dementia collected within
Betula, however, are not included in the Linnaeus database.

**Measures**

**Dementia and AD (Studies I & II).** Dementia status is available on an
annual basis for most of the participants in the Betula project. The currently
available information about dementia status covers the years 1989 to 2010.
Diagnoses were established in accordance with the criteria of the DSM-IV
(American Psychiatric Association, 2000). The analyses were conducted by a
clinical research and geriatric psychiatrist who performed several
prospective and retrospective analyses of the information that was available
at each test wave. This included comprehensive analysis of various general
and specific health measures, results from neuropsychological testing, and
clinical course. In addition, data have been blindly assessed to increase the
validity of cognitive status. The clinical course over time is of importance
when establishing diagnoses, and thus, in 2010, the data were re-analyzed
and clinical course were related to the cognitive status at the inclusion of the
study. Incorrectly included participants (T1-T5) accounted for only 0.4% of
all the participants, which indicates a high validity of dementia diagnosis. In
Studies I and II, when using dementia as an outcome variable, all types of
dementia were used, including AD, VaD, DLB, FTD, PDD, and NUD. For
Studies I and II, AD was also used as a dependent variable. Dementia and
AD were coded in the same way (coded as 1) in both studies when compared
to the non-demented (coded as 0).

**Episodic memory (Study III).** The following episodic memory measures
from the Betula study were included in Study III (for a detailed description,
see Rönnlund & Nilsson, 2006b).
- Recall of sentences: the participants were shown sixteen written sentences, each for eight seconds. The sentences were also read aloud by the experimenter. This was followed by free recall of as many sentences as possible directly after.
- Recall of actions: A total of 16 different actions were performed with different objects, and each action was performed for eight seconds. This was followed by free recall directly after.
- Category cued recall: Following the free recall tasks described above, participants were asked to recall as many nouns as possible presented either among sentences or actions. Eight semantic categories presented on a sheet served as cues for the recollection.
- Recall of nouns: A list of 12 nouns was presented at a pace of 2 seconds per item, and participants were asked to recall as many nouns as possible in any order at the same rate (2 seconds per item).
- Activity recall: At the end of the test session, the participants were asked to recall as many of the tasks as possible, in any order, that they had performed during the test session. The total number of recalled tasks served as the score for the test.

A unit-weighted (z) episodic memory composite score was computed based on the scores for each measure. The test-retest (stability) coefficients for the composite score were \( r = .75 \) (\( p < .01 \)) and \( r = .73 \) (\( p < .01 \)) for 5-year and 10-year follow-ups, respectively.

**Semantic memory (Study III).** Four individual measures were used as indicators of semantic memory (cf. Nyberg et al., 2003). Three of them were verbal fluency tasks requiring the participants to generate as many words as possible during one minute. The restrictions were as follows: generate words with the initial letter A (not names), words beginning with the letter M and containing five letters (not names), and professions beginning with the letter B. The fourth task used to measure semantic memory was the SRB, a 30-item multiple-choice synonym test (Dureman, 1960) in which the participants are asked to underline the correct synonym of each target word. Each target has five alternatives. The time limit for the task is seven minutes, and the number of correctly identified synonyms is used as the score for the test. A semantic composite (z) score was computed based on the four indicators. The stability coefficient for the semantic composite score was \( r = .785 \) (\( p < .01 \)) for the 5-year follow-up and \( r = .751 \) (\( p < .01 \)) for the 10-year follow-up.

**Visuospatial ability (Study III).** The WAIS-R Block Design Test (Wechsler, 1981) was used as a measure of visuospatial ability. The task requires a set of four or nine bicolored blocks. The participants are required to use the blocks to duplicate a maximum of nine target patterns presented
in order of ascending difficulty. A raw score is generated based on the number of trials and time to complete the patterns. The scores for the present purposes were transformed to z-scores. Cronbach’s α of .82 has been reported for this test in a Betula sample (Rönnlund & Nilsson, 2006a). The stability coefficient for visuospatial score was $r = .78$ ($p < .01$) for the 5 year follow-up and $r = .76$ ($p < .01$) for the 10-year follow-up.

**Leisure activities (Study 1).** In a questionnaire, which was sent to the participants about a week prior to their health examination for the Betula study, the participants indicated how often they engaged in 16 different leisure activities during the past three months. The activities were Travel/Trips; Sports/Exercise/Walking in the forest; Hunting/Fishing; Reading books; Reading magazines; Reading newspapers; Watching TV/Listening to the radio; Movies/Concerts/Theater; Restaurant visits; Spending time with family, relatives, and friends; Attending courses/workshops; Religious assemblies; Association work; Playing musical instruments; Needlework; and Other Hobbies/Activities.

The participants rated their activity frequency level on an ordinal scale ranging from never (coded as 0), occasionally (1), a few times a month (2), sometime per week (3), or every day (4). To obtain a meaningful number of observations, however, a new classification scale was made ranging from never (coded as 0), occasionally or a few times a month (1), and sometime every week or every day (2). Of the participants, 97.1% reported that they read the newspaper every day, and 98.3% that they watched TV/listened to the radio daily. Due to extreme skew, these two questions were not recoded and were excluded from further analyses.

Using these new classifications, a "total" index (maximum 28 points) was computed based on the sum score of all 14 activities. To investigate whether different dimensions of leisure activities are associated with incident dementia, participants from Sample 5 ($M = 67$ years) of the Betula study were asked to estimate if an activity was predominantly “mental,” “social,” or “physical.” A questionnaire was sent out where participants rated every activity on a scale from 1 to 10 for each of these three dimensions. Based on responses from 18 participants, two indexes were computed. The "mental" index included Read books; Read magazines; Movies/Concerts/Theater; Play musical instruments; Needlework; and Hunting/Fishing (max 12 points), and the "social" index included Travel/Trips; Restaurant visits; Spend time with family, relatives, and friends; Attending courses/workshops; Religious assemblies; and Association work (max 12 points). Only one activity, Sports/Exercise/Walking in the forest, was regarded as predominantly physical. Thus, no index was generated to represent physical activity.
Cronbach’s \( \alpha \) for the Social Index was .49, for the Mental Index .23, and for the total index .59.

**Social relationships (Study II).** Data from five questions about social relationships collected in the Betula study were used: (1) Living status (Living with Wife/Husband/Common law spouse/Children/Sibling or Other person = (coded as) 1/, living alone = 0), (2) “Do you have any really close friends whom you can contact and talk to about anything?” (yes = 1/no = 0), (3) “Do you think you meet your friends and acquaintances often enough?” (yes = 1/no = 0), (4) “How often do you visit or are visited by your friends and acquaintances?” (Daily/Several times a week/Once a week/Between once a week and once a month/Between once a month and once a quarter/Less than once a quarter/Never), and (5) “How often do you have contact with your friends and acquaintances in other ways than visits?” for example, by telephone (Daily/ Several times a week/Once a week/Between once a week and once a month/Between once a month and once a quarter/Less than once a quarter/Never). To obtain a meaningful number of observations regarding the two latter questions about visits and contact frequency, a new classification was made into once a week or more, (coded as 1), and less than once a week (0). Finally, an index was computed as the sum of scores for the entire set of relationship variables (maximum 5 points).

**Social network size (Study III).** Four questions collected in the VIP as part of a questionnaire designed to measure social relationships were used as indicators of social network size. The questions were: (1) “How many persons do you know and have contact with that have the same interests as you?”, (2) “How many persons, that you know, do you meet or talk with during a regular week?”, (3) “How many friends do you have that can come into your home at any time and feel at home?”, and (4) “How many are there, in your family and among your friends, with whom you can talk freely without reflection?” For each of the questions, the participants were requested to indicate the relevant number on a scale having the following alternatives: nobody (coded as 0), 1-2 persons (1), 3-5 persons (2), 6-10 persons (3), 11-15 persons (4), and more than 15 persons (5). An index for network size was computed as the sum score of the four questions (max = 20; Cronbach’s \( \alpha = .77 \)).

Different covariates were used for the three studies as shown in Table 2. For Study III, which used data from Betula and VIP linked in the Linnaeus database, all the information collected in Betula is not available.
Table 2. Variables used as covariates in the different studies included in this thesis.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gender</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Years of education</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Marital status</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subjective health</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Stress</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Genetics</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global cognitive status</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Note: Detailed description for each variable is in the main text*

Potential confounders (source in brackets):

- **Age** (Betula).
- **Gender** (Betula).
- **Years of education** (Betula).
- **Marital status** (Betula). Coded as four different categories: married-cohabiting/unmarried/divorced/ or widow-widower.
- **Cardiovascular risk factors** (Betula). A sum of four self-reported diseases/conditions was used: high blood pressure (yes/no), stroke (yes/no), incidence of heart attack/cardiovascular problems (yes/no), and diabetes (yes/no).
- **Subjective health** (VIP). Rating of health status during the last year, ranging from “very good”, “quite good”, “reasonably”, “rather poor”, to “poor.” For the analyses, rather poor and poor were coded as 0, and reasonably, quite good, and very good were coded as 1.
- **Smoking** (Betula). Do you smoke, or used to, practically daily? (yes/no).

- **Alcohol consumption** (Betula). In Studies I and II, three categories were used: currently drink, never drank, or, have quit drinking. In Study III, two categories were used: currently drink, or never drank - have quit drinking.

- **Physical activity** (VIP). Participants rated frequency of participation in exercise “within the last three months, wearing an exercise outfit, with the purpose of improving physical status or to feel good” on a scale ranging from never, now and then but not regularly, once a week, 2–3 times per week, or more than 3 times a week. A dummy variable was generated as a measure of low activity (never, now and then but not regularly) and high activity (once a week or more).

- **Obesity** (Betula). BMI ≥ 30 was treated as obesity and was compared to BMI <30.

- **Stress** (Betula). The question was asked, “Do you in general feel stressed?” (yes/no).

- **Depressive symptoms** (Betula). In Study I: Feelings of depression (yes/no). In Studies II and III: Index of depressive symptoms, calculated by the sum of six self-reported measures: (1) often feel lonely, (2) often feel dispirited, (3) feeling anxious, (4) loss of appetite, (5) difficulty sleeping, and (6) fatigue.

- **Genetics** (Betula). APOE genotyping was performed by using polymerase chain reaction. The APOE genotype was categorized based on the presence of at least one ε4 allele as compared to non-carriers. The ε2/ε4 combination was not included in the analyses because it has been suggested that the ε2 allele might be protective (Corder et al., 1994).

- **Global cognitive status** (Betula). Mini Mental State Examination (MMSE, Folstein et al., 1975) was used as an estimation of global cognitive status. The measure was originally developed for screening and identification of dementia, not as a diagnostic test, but rather as an indicator of cognitive status.
Summary of Study I


Aim
To investigate the association between participation in various leisure activities in old age (≥65 years) and the risk of incident dementia.

Participants
The number of participants aged 65 years or older at baseline was 1,812. Participants who had not answered the questionnaire about leisure activities (n = 58), who were lost at follow-up (n = 41), had dementia at inclusion (n = 19), who died during the first five years after baseline (n = 209), and a few subjects diagnosed with dementia shortly after the last follow-up examination in 2010 (n = 10) were excluded. Thus, a total of 1,475 elderly (836 females, 639 males) 65 years or older (M = 73.70 years, SD = 6.85 years) were included in the analyses. The participants belonged to Sample 1 (n = 314), Sample 2 (n = 344), Sample 3 (n = 383), Sample 4 (n = 217), and Sample 5 (n = 217) in the Betula study.

The relatively large number of unanswered questions about leisure activities on the questionnaire was because the participants had to fill it out at home. Within this group of participants were individuals from Sample 1 which had become demented at the time of T2 (baseline for Sample 1 in this study). The reason for excluding participants who had died (without having developed dementia) 1–5 years after baseline was to minimize the risk of including non-demented persons who were less active as a consequence of poor health, and thus reducing the plausible effects that an active lifestyle might have on cognition. The reason to exclude those who were lost to follow-up (for example, those who moved outside the catchment area) was to ensure that all participants could be regarded as either demented or non-demented over the entire follow-up period. For this study, participants who developed dementia shortly after the last assessment (2010) were excluded. This decision was made on the assumption that it would be incorrect to consider people who became demented shortly after the study end as non-demented in the analyses, although the end-date for this study was set at the end of the last follow-up examination.

The fact that 65 years was chosen as baseline age was partly motivated by the fact that 65 is the most common retirement age in Sweden. This gives more similar opportunities for engagement in leisure activities. This age is also interesting because it is around this age (age 60–65) that
episodic memory functioning, in general, begins to deteriorate (Rönnlund et al., 2005).

**Statistical procedure**

Because questions about leisure activities were included in the Betula project at T2 (1993–95), and because some samples (S4, S5) were first included at later test occasions, it was necessary to adapt the design of this study to account for this. For Sample 1, which participated at T1 (1988–1990) leisure activity data were available first at T2, whereas for Samples 2 and 3 (T2, 1993–1995), Sample 4 (T3, 1998–2000), and Sample 5 (T4, 2003–2005), the questionnaire was answered the first time individuals participated in the study. Because the time when answering questions regarding leisure activities for the first time differed depending on sampling, the data were adjusted to get a common baseline for all participants (i.e. the first time participants answered the questionnaire) to be able to include as many participants as possible in the study. The design of Study 1 is presented in Figure 2.

![Diagram](image)

**Figure 2.** Design of the analyses over three time periods. Those having dementia within every time period were compared with those without dementia. The number of cases with dementia is shown in the boxes.
Although the returnee rate in the Betula study is high in general (78-86%), not all samples return (due to design), and thus longitudinal data are not available for all samples regarding health, leisure, and cognitive measures. Longitudinal follow-up regarding dementia status is, however, available for all samples. The long follow-up made it possible to examine the longitudinal effects of leisure, not only over the total follow-up period, but also 1–5 years, 6–10 years, and 11–15 years after baseline to see whether or not effects differed between the various time intervals and in order to take into account whether or not reverse causation could confound the results. Samples 1–3 could be included in analyses of three intervals (1–5 years, 6–10 years, and 11–15 years). Sample 4 was included in two intervals (1–5 years and 6–10 years), and Sample 5 was included in one interval (1–5 years).

Cox proportional hazard regressions were used in the analyses, and time-to-event was calculated from date of health assessment to the year of (1) dementia diagnosis, (2) death, or (3) date of the end of follow-up (2010). Survival time was rounded down to the nearest whole year. For example, an individual in Sample 5 could have a survival of almost six years, but this was then rounded down to 5 years. This also corresponds well to the test intervals used in the Betula project (every fifth year). Participants who developed dementia during any of the time intervals were never used as healthy controls in the analysis of other time intervals. However, subjects who never developed dementia could serve as healthy controls in analyses of several time periods. Furthermore, participants who died during any time period were not used as controls in the analysis of that period. Hence, the analyses of each period consisted only of participants who either became demented or those who survived the entire period without having dementia.

Results
Over the total follow-up period, 357 incident dementia cases were identified. Among those who received a diagnosis of dementia were 162 diagnosed 1–5 years after baseline, 139 participants 6–10 years after baseline, and 56 cases that were identified during the last time-period, 11–15 years after baseline. Over the same periods, there remained 1,118 (1–5 years), 682 (6–10 years), and 404 (11–15 years) participants who were dementia free. Overall, those who developed dementia were, compared with those who remained without dementia, older, females, less often married, less frequent users of alcohol, and carriers of the APOE ε4 allele.

Results from the Cox proportion regression analyses investigating the associations between leisure activities and dementia are presented in Table 3.
After controlling for all potential confounders (age, gender, education, diseases, smoking, alcohol use, marital status, general stress, feelings of depression, and APOE genotype), the results from the analyses of the total time period showed that higher levels in the “Social” and “Total” activity indexes were associated with decreased risk of dementia in old age. The “Mental activity” index was not associated with decreased risk of dementia in old age. Analyses of the separate time periods after baseline (1–5 years, 6–10 years, and 11–15 years), however, only revealed significant associations for these indexes in the first time period (1–5 years) after baseline. Analyses combining the second and third periods after baseline did not alter the results. Thus, results from this study provide little support that engagement in leisure activities protects against dementia across a longer time frame. Effects found for the first time period might indicate positive short-term effects, but might also reflect reverse causality, suggesting that that the preclinical phase of dementia influences the level of engagement in leisure activities. It should be noted that potential associations depending on APOE status were also examined. In addition, separate analyses with AD as the outcome were also performed. These analyses, however, did not change the pattern of the results. Although not presented in the article of study I, results showed that higher age and being an ε4-carrier were factors that had the strongest negative associations with all-cause dementia and AD across a longer time frame. In some models, marital status (widowed, but not single or divorced) turned out to be a risk factor for dementia, whereas female gender was a risk factor for AD.
Summary of Study II


**Aim**

To investigate the association between various aspects of social relationships in old age (≥65 years) and risk of incident all-cause dementia and AD.

**Participants**

A total of 1,769 non-demented participants took part in a health assessment at baseline, and this was when questions about social relationships were asked. Participants who did not answer the questions about social relationships (n = 19), had missing data on the MMSE (n = 2) and obesity (n = 10), or who had a survival time of less than one year after health assessment (n = 23) were excluded. Thus, the final sample consisted of 1,715 participants (958 women, 757 men) who were 65 years or older (M = 74.20 years, SD = 7.01 years). Participants were from Sample 1 (n = 382), Sample 2 (n = 382), Sample 3 (n = 448), Sample 4 (n = 249), and Sample 5 (n = 254) of the Betula study. The main reason to use 65 years as baseline age was the same as in Study I.

For this study, it was decided to include individuals who were diagnosed with dementia shortly after the study end (n = 10) and participants who were lost to follow-up. The year of this event was set as the end date when survival time was calculated. Although the actual outcome over the whole follow-up period was unknown for those lost to follow-up, in comparison to other participants, it was decided that it could be relevant to include them based on the time they participated. Time to event for each individual was calculated from date of health assessment to the year of (1) dementia diagnosis, (2) lost to follow-up, (3) death, or (4) the end of follow-up.

**Statistical procedure**

Because questions about social relationships were included in the Betula study at T2 (1993–95), and because some samples (S4, S5) were first included at later test occasions, the data were adjusted to get a common baseline (similar to Study I). The design of the study is presented in Figure 3.
Figure 3. The design of Study II. All cases of dementia, as well as AD separately, were compared to the non-demented in the analyses over the total follow-up period. Analyses were also performed with delayed entry as indicated by blue arrows.

In addition to analyses of the total follow-up period after baseline measurement (up to 16 years), analyses were performed with delayed entry. In these analyses, participants with short survival time were excluded. This was performed to adjust for reverse causality and to isolate long-term effects. The results from Study I, and limitations regarding directionality in previous studies (see Pillai & Verghese, 2009) motivated this.

Cox proportional hazard regressions were used to investigate possible associations. In analyses with delayed entry, entry time after assessment of social relations was moved forward stepwise by one year at a time. Because only participants with at least one survival year were included in this study, the first time point of delayed entry was set at 2 years.

Results
Over the total follow-up period (16 years), 373 incident cases of dementia were identified, including 207 cases of AD. Concerning baseline characteristics, those who developed dementia and AD were more often of female gender, did not drink alcohol, lived alone, and had lower mean values on both the MMSE and on the relationship index. In addition, participants with all-cause dementia were older at baseline compared to those without dementia, whereas obesity was less common among participants with
incident AD. Also, AD cases had a lower frequency of cardiovascular risk factors at the group level in comparison with controls. The results from the Cox proportion regression analyses investigating associations between social relationships (living status, contact and visit frequency, satisfaction with contact frequency, having/not having a close friend, and social relationship index) in old age and risk of dementia and AD are presented in Tables 4 and 5 respectively.

Table 4. Associations between social relationship variables and all-cause dementia presented as hazard ratios (HR).

<table>
<thead>
<tr>
<th></th>
<th>ALL-CAUSE DEMENTIA</th>
<th>ALL-CAUSE DEMENTIA</th>
<th>ALL-CAUSE DEMENTIA</th>
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<td></td>
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<td>≥ 3 years (n = 1545)</td>
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<td></td>
<td>HR (95% CI)</td>
<td>p-VALUE</td>
<td>HR (95% CI)</td>
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<td></td>
</tr>
<tr>
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<td>-</td>
<td>Reference level</td>
</tr>
<tr>
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<td>Having a close friend</td>
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<tr>
<td>No</td>
<td>Reference level</td>
<td>-</td>
<td>Reference level</td>
</tr>
<tr>
<td>Yes</td>
<td>0.82 (0.60-1.11)</td>
<td>0.199</td>
<td>0.85 (0.61-1.17)</td>
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<td>Meet friends and acquaintance</td>
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</tr>
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<td>Reference level</td>
</tr>
<tr>
<td>Yes</td>
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<tr>
<td>acquaintances</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Less than once a week</td>
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<td>-</td>
<td>Reference level</td>
</tr>
<tr>
<td>Once a week or more</td>
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<td>Less than once a week</td>
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<tr>
<td>Once a week or more</td>
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<td>0.96 (0.68-1.35)</td>
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<td>0.88 (0.79-0.98)</td>
<td>0.019</td>
<td>0.89 (0.79-0.99)</td>
</tr>
</tbody>
</table>

All analyses adjusted for age, gender, years of education, MMSE, cardiovascular risk factors, obesity, alcohol use, smoking status, stress, and depressive symptoms.
Table 5. Associations between social relationship variables and AD presented as hazard ratios (HR).

<table>
<thead>
<tr>
<th>Relationship Index</th>
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<td></td>
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<td>HR (95% CI) p-VALUE</td>
<td>HR (95% CI) p-VALUE</td>
</tr>
<tr>
<td>Living with someone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference level -</td>
<td>Reference level -</td>
<td>Reference level -</td>
</tr>
<tr>
<td>Yes</td>
<td>0.80 (0.59-1.09) 0.161</td>
<td>0.75 (0.55-1.03) 0.080</td>
<td>0.74 (0.53-1.03) 0.076</td>
</tr>
<tr>
<td>Having a close friend</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference level -</td>
<td>Reference level -</td>
<td>Reference level -</td>
</tr>
<tr>
<td>Yes</td>
<td>0.72 (0.48-1.07) 0.105</td>
<td>0.77 (0.50-1.17) 0.214</td>
<td>0.77 (0.50-1.18) 0.235</td>
</tr>
<tr>
<td>Meet friends and acquaintances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference level -</td>
<td>Reference level -</td>
<td>Reference level -</td>
</tr>
<tr>
<td>Yes</td>
<td>0.93 (0.61-1.42) 0.735</td>
<td>0.92 (0.59-1.43) 0.709</td>
<td>1.00 (0.63-1.60) 0.944</td>
</tr>
<tr>
<td>Visiting/Visits of friends and acquaintances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than once a week</td>
<td>Reference level -</td>
<td>Reference level -</td>
<td>Reference level -</td>
</tr>
<tr>
<td>Once a week or more</td>
<td>0.78 (0.56-1.07) 0.127</td>
<td>0.85 (0.61-1.20) 0.358</td>
<td>0.87 (0.61-1.24) 0.431</td>
</tr>
<tr>
<td>Contact with friends and acquaintances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than once a week</td>
<td>Reference level -</td>
<td>Reference level -</td>
<td>Reference level -</td>
</tr>
<tr>
<td>Once a week or more</td>
<td>0.92 (0.59-1.45) 0.719</td>
<td>0.99 (0.61-1.61) 0.973</td>
<td>1.00 (0.61-1.64) 0.991</td>
</tr>
<tr>
<td>Relationship index</td>
<td>0.85 (0.73-0.98) 0.025</td>
<td>0.86 (0.74-1.00) 0.056</td>
<td>0.87 (0.74-1.02) 0.090</td>
</tr>
</tbody>
</table>

All analyses adjusted for age, gender, years of education, MMSE, cardiovascular risk factors, obesity, alcohol use, smoking status, stress, and depressive symptoms.

The results from the analyses of the entire follow-up period revealed that higher values on the relationship index were associated with reduced risks of both dementia and AD, a result that persisted after controlling for all potential covariates (age, gender, years of education, cardiovascular risk factors, obesity, alcohol use, smoking status, stress, and depressive symptoms). Furthermore, visiting/visits of friends and acquaintances more than once a week was related to decreased risk for all-cause dementia but not for AD.

In the analyses with a delayed entry set to 2 years, 81 participants were excluded with too short survival time (cases of all-cause dementia = 27, without dementia = 54) resulting in a sample of 1,634 individuals. From the sample (n = 1,549) investigating the association with AD, 69 participants (AD = 15, without AD = 54) were excluded resulting in a sample of 1,480 individuals. The results revealed that the social relationship index was the only variable that was associated with dementia (only all-cause dementia). When entry was set to 3 years, 89 participants (cases of all-cause dementia = 29, without dementia = 60) had to be excluded resulting in a sample of 1,545 participants. In analyses exclusively with AD, 71 participants were additionally excluded (AD = 11, without AD = 60) resulting in a sample of 1,409 individuals. In these analyses, none of the indicators were significant for either all-cause dementia or AD. Thus, although the results from this
study show that certain aspects of social relationships can be associated with incident dementia or AD, it is plausible that these associations reflect reverse causality.

Although not presented in the article for Study II, analyses including only participants with relatively long survival time (≥5 years) after baseline before any event occurred showed that higher age and being an ε4-carrier (separate analyses including APOE data were performed) were the strongest risk factors for all-cause dementia and AD across a longer time frame, although it should be noted that the number of participants significantly decreased in the analyses Furthermore, female gender was associated with higher risk of AD, whereas obesity (BMI ≥ 30) was associated with reduced risk of both all-cause dementia and AD.

**Summary of Study III**


**Aim**
To investigate the association between social network size and cognitive ability in a middle-aged (40–60 years) sample.

**Participants**
In study III, all of the participants had taken part in both the Betula study and the VIP. The Linnaeus database was examined because participants from Betula and VIP are linked within this database at the individual level. The age range was restricted to 40–60 years due to the design of the VIP in which participants are tested at 40, 50, and 60 years of age. Data from T2 (1993–1995), T3 (1998–2000), and T4 (2003–2005) in Betula were used because information on cognitive function (Betula) and social network size (VIP) were linked across these periods. A selection criterion was participation in the two studies within a span of 12 months. The first time fulfilling this criteria during any test occasion constituted the baseline for the participant. The final sample was obtained after excluding individuals with incomplete data on social network size (n = 14), cognition (n = 4), education (n = 12), physical exercise (n = 3), subjective health (n = 4), or use of alcohol (n = 1). Thus, a total of 804 middle-aged participants (448 females, 356 males) from Samples 1–3 who were 40–60 years old (M = 52.17 years, SD = 7.59 years) at baseline were included in the study.
**Statistical procedure**

Data were adjusted to get a baseline, including participants who were tested in the two studies within a span of 12 months. The design and flowchart of Study III is presented in Figure 4.

![Figure 4. The design and flowchart of the study. Participants were tested every fifth year in the Betula study and every tenth year in VIP.](image)

- Due to the study design, some participants from Sample 3 in the Betula study were not re-tested.
- Dropouts are participants who were deceased or did not want to participate at the follow-up measurement.
- For some participants, 10-year follow-up information regarding social network size was also available.

For a number of participants, 5-year \( (n = 604) \) and 10-year \( (n = 255) \) cognitive follow-ups were available. For some subjects \( (n = 131) \), 10-year follow-up information on both social network size and cognitive functioning was available (within a span of 12 months). This allowed for both cross-sectional and longitudinal analyses of the effects of network size on cognitive performance, although the number of individuals decreased considerably with time.

Hierarchical multiple regression analyses were employed to examine the relationship between network size and cognitive functioning. The
hierarchical entry of variables was used to sort out the influence of other independent variables (demographic, health, and lifestyle factors) before assessing the contribution of network size on measures of cognitive functioning (episodic memory, semantic memory, and visuospatial ability). This was found to be suitable because the independent variables correlated with each other to a varying degree and also correlated with the cognitive measures. Cross-lagged panel correlations were used to investigate the directionality between network size and cognitive functioning among those participants (n=131) with longitudinal data for both of these factors.

**Results**

Dropout analysis revealed that the 604 returnees at the 5-year follow-up did not differ significantly in regard to background characteristics compared to the non-returnees (n = 200), except that the returnees had a lower mean score on the depressive symptom index. The 255 participants who were re-assessed at the 10-year follow-up were younger and exhibited fewer depressive symptoms than non-returnees (n = 549).

The results from the hierarchical multiple regression analyses investigating associations between social network size and three cognitive abilities (episodic memory, semantic memory, and visuospatial ability) are summarized in Table 6.

**Table 6. Results from analyses investigating associations between social network size and cognitive functioning.**

| Predictor | Episodic Memory | | Semantic Memory | | | Visuospatial Ability |
|-----------|-----------------|-----------------|-----------------|-----------------|-----------------|
|           | ΔR²             | β               | ΔR²             | β               | ΔR²             | β               |
| **Cross-sectional (n=804)** | | | | | | |
| ³Step 3 † | .005*           | .009**          | .007*           | | | |
| Network Size | .074*          | .099**          | .088*           | | | |
| Total R² | .298***         | .275***         | .168***         | | | |
| **Five Year Follow-up (n=604)** | | | | | | |
| ³Step 4 † | .002³           | .003*           | .002            | | | |
| Network Size | .046³         | .058*           | .047            | | | |
| Total R² | .603***         | .635***         | .645***         | | | |
| **Ten Year Follow-up (n=255)** | | | | | | |
| ³Step 4 † | .007*           | .010*           | .001            | | | |
| Network Size | .088*          | .104*           | .032            | | | |
| Total R² | .588***         | .592***         | .629***         | | | |

*Step 1 controlled for age, gender, and education. Step 2 controlled for subjective health, depressive symptoms, physical exercise, and alcohol use.

³Step 1 controlled for cognitive performance at baseline. Step 2 controlled for age, gender, and education. Step 3 controlled for subjective health, depressive symptoms, physical exercise, and alcohol use.

ΔR²: R Square Change, β: Standardized Beta.

*p < .05, **p < .01, ***p < .001, †p = .088

59
Results from the cross-sectional analyses demonstrated a positive association between social network size and cognitive performance, and this association was observed across the three cognitive abilities. In contrast, for time-related changes the baseline network size was only positively related to 5-year changes in semantic memory, although almost reaching significance for episodic memory. At the 10-year follow-up, the baseline network size was associated with changes in both semantic and episodic memory but was still unrelated to changes in visuospatial performance. Other factors associated with cognitive change above baseline cognitive performance were age (5-year change in episodic memory and visuospatial ability and 10-year change in all constructs), female gender (5-year and 10-year change in episodic memory), education (5-year change in all constructs), and physical exercise (5-year change in semantic memory).

For a small portion of participants (n = 131), 10-year follow-up data were available for network size. Cross-lagged panel correlations showed that baseline network size was associated with future performance in semantic memory as well as episodic memory. None of the abilities, however, were related to future network size. Thus, the results from this study provide support for a positive relationship between social network size and future performance in declarative memory abilities. The results are in accordance with the cognitive reserve model (Stern, 2002), suggesting that higher levels of cognitive stimulation, such as having a more extensive social network, have beneficial long-term effects on cognitive functioning.

General discussion
The overarching aim of this thesis was to investigate if aspects of social relationships and leisure activity can affect memory functioning and the risk of incident dementia. To this end, longitudinal data from the Betula project and VIP were analyzed.

In Study I, higher levels of social leisure activity and total activity in old age (≥ 65 years) were associated with reduced risk of dementia over a follow-up period of 15 years. The findings are consistent with previous findings that a higher degree of participating in leisure activities late in life reduces the risk of dementia (for reviews, see Fratiglioni et al., 2004; Stern & Munn, 2010; Wang et al., 2012). In Study II, social relationships (frequent visiting/visits of friends and higher levels on a relationship index) were associated with reduced risk of dementia and AD. These results are in agreement with some other studies showing a higher level of participation in social relationships to be associated with lower risk of dementia and AD (e.g., Bickel & Cooper, 1994; Crooks et al., 2008; Fratiglioni et al., 2000; Helmer et al., 1999).
In both Studies I and II, however, the observed association was no longer significant after removing from the analyses cases with dementia shortly after baseline (Study I, up to five years; Study II, up to three years). Thus, although protective short-term effects cannot be excluded, the observed associations might be due to reverse causality. Study III, however, showed that social network size was positively related to cognitive change (episodic memory and semantic memory) over a follow-up period of 10 years in a middle-aged sample (40–60 years), although the explained variance was small. Together, the results presented in this thesis do not provide strong support for the cognitive reserve hypothesis in relation to dementia. However, in terms of cognitive functioning there is at least a weak association, and this is in line with the prediction that social networks might stimulate aspects of memory and thereby reduce or delay the onset of the age-related decline.

Results in relation to the cognitive reserve hypothesis
Although the results from Studies I and II do not provide strong support for the cognitive reserve hypothesis, Study III showed that social network size was associated with cognitive change. The beneficial effects are opposite to the only prior study that we know of (Green et al., 2008) that also targeted middle-aged ($M = 47.3$ years at baseline), because they did not find that social network size was associated with cognitive change (MMSE, delayed recall). Considering the fact that onset of decline, at least in “fluid” abilities (e.g., speed of processing, visuospatial ability), starts in late middle-age (e.g. Rönnlund & Nilsson, 2006a; Rönnlund et al., 2005; Schaie, 1994), the results of Study III are interesting. If social network size can moderate the negative age-related influence on declarative memory functions and promote growth and reduced negative changes in regions vital for these abilities, such as the neocortex and the hippocampus (Moscovitch et al., 2005), a larger social network might put an individual on a cognitive trajectory that is beneficial in old age. Considering that semantic ability is quite robust even in old age and episodic memory is more age-sensitive (Rönnlund et al., 2005), the results are promising because effects were found also for episodic memory. It is also important to note that middle age is often characterized by a steady decrease in the number of friendships (Wrzus et al., 2013).

When also taking into account the covariates used in studies, it should be noted that education, a well-established cognitive reserve index that has been associated with both dementia (for review, see Valenzuela & Sachdev, 2006) and cognitive functioning (e.g., Farmer, Kittner, Rae, Bartko, & Regier, 1995; Lyketsos, Chen & Anthony, 1999), was not a robust predictor in any of these three studies. In Study III, years of education were positively associated with 5-year memory changes (episodic, semantic, and visuospatial), but not with 10-year changes. It should be noted that Sharp
and Gatz (2011) in their review reported a relatively even distribution between studies that observed (58%) and did not observe (42%) a significant association between educational attainment and risk for dementia. Physical exercise, previously related to cognitive functioning (e.g., Etnier et al., 1997) and a factor that can potentially create a cognitive reserve, was not associated with cognitive change over 10 years. Thus, considering all variables used in these three studies, few can be said to support the cognitive reserve hypothesis.

To put a counterweight to the lack of impact from factors that have been associated with the cognitive reserve, however, other factors previously associated with cognitive functioning such as depressive symptoms (e.g., Zelinski & Gilewski, 2004) and alcohol use (Anstey et al., 2009) were unrelated to cognitive change over 10 years in Study III. Similarly, in Studies I and II, few covariates were associated with dementia, although it should be noted that the results are mixed regarding, for example, smoking (for review and meta-analyses, see Cataldo et al., 2010; Peters et al., 2008), alcohol use (for review and meta-analyses, see Anstey et al., 2009; Peters et al., 2008), stress (Sundström et al., 2014), and depressive symptoms (e.g., Becker et al., 2009; Lindsay et al., 2002) in relation to dementia and AD.

An important question is whether beneficial effects of cognitive stimulation should be expected. Even if many studies have used similar age groupings as the ones included in this thesis and reported different outcomes, it might be important to point out that the average baseline age for the participants was relatively high, at least in Study I (73.70 years) and Study II (74.20 years). Results from these showed, overall, although not all of this was not presented in the articles, that age and ApoE-ε4 status were the strongest predictors of AD and all-cause dementia and that female gender was related to AD. APOE status has previously been associated with both all-cause dementia and AD (Farrer et al., 1997; Frisoni et al., 1994; Stengard et al., 1995; Treves et al., 1996), whereas female gender has been related to higher risk of AD (Andersen et al., 1999; Gao et al., 1998).

Results of this thesis raise the question of whether or not it is possible that in old age genetics and other fixed factors become more prominent predictors or whether or not the cognitive trajectory is more or less set when reaching old age. In line with the cognitive trajectory being more or less set, study findings show that the genetic influence on cognitive functioning increases steadily over time from childhood to old age (Plomin & Petrill, 1997). It should be noted, though, that being widowed (but not single or divorced) and being non-obese were associated with higher risk in some models. This is in agreement with some previous studies regarding widowhood (e.g., Sundström et al., 2014) and studies showing that high BMI is associated with reduced risk in old age (Fitzpatrick et al; 2009) because
low BMI can be a part of the prodromal phase of dementia (Buchman et al., 2005; Johnson et al., 2006).

**Support for an active or passive model?**
In this thesis, the cognitive reserve model was investigated from the perspective of an active model. Our results did not reveal any long-term effects of enrichment factors undertaken in old age. Associations were found when investigated earlier in life (midlife), although they were moderate. Thus, following this pattern, it is reasonable that enrichment factors undertaken at even younger ages have a larger impact on cognitive functioning given that brain plasticity is greater in youth or early adulthood. Furthermore, it is not hard to believe that the formation of brain networks and cognitive components created earlier in life have larger impacts in old age.

In the present studies, it was not possible to link activity levels in young adulthood or middle age to cognitive functioning in old age. Even if previous studies have suggested that midlife or early life engagement in leisure activities (e.g. Carlson et al., 2008; Crowe et al., 2003; Friedland et al., 2001; Fritsch et al., 2005) and social relations (Håkansson et al., 2009) are associated with decreased risk of dementia, an important question is still how much and when the cognitive reserve is modificable over the life course. Longitudinal data (e.g. Rönnlund et al., 2005) support the idea that several cognitive functions seem to be relatively stable over the life course (e.g. episodic and semantic memory) until reaching old age, but there is little support for significant increment in capacity, at least for fluid abilities, after the age of 20 (see Park et al., 2002). Based on this, a logical assumption is that cognitive capacities in general only significantly improve before reaching adulthood. Thus, is it possible that the cognitive reserve follows the same pattern? For psychometric intelligence, it has, for example, been found that the correlation between performance on a manifest intelligence test taken at age 11 and age 77 is as high as $r = .63$ (Deary, Whalley, Lemmon, Crawford, & Starr, 2000). Similarly, other studies have reported high correlations in cognitive/intellectual performance between different ages, for example $r = .68$ between the ages of 14 and 42 (Kangas & Bradway, 1971) and $r = .78$ between the ages of 19 and 61 (Owens, 1966). Furthermore, there are studies suggesting that mental abilities during childhood (e.g. Whalley, Starr, Athawes, Hunter, Pattie, & Deary, 2000) and young adulthood (e.g. Snowdon, Kemper, Mortimer, Greiner, Wekstein, & Markesbery, 1996) can be associated with future cognitive functioning and risk of dementia.

If future cognitive functioning can be predicted by neurological components established earlier in life, the brain reserve concept (Katzman, 1988; 1993) to some degree seems applicable. Karama et al (2014), for example, found that cognitive ability in childhood (11 years), accounted for
more than two-thirds of the relationship between cognitive ability (70 years) and cortical thickness (73 years) in old age, an indicator that can be used for the passive models. Cortical tissue volume is often assumed to be related to cognitive function. The authors suggested that future studies on cognitive aging should, if possible, take into account cognitive status in childhood. However, Pillai et al. (2012), for example, aimed to investigate whether educational level could be related to cortical thickness in old age. The results showed a pattern opposite to that expected, i.e., that higher education instead was associated with a thinner cortex. Furthermore, the degree of atrophy in brain regions related to intellectual variability showed no difference between educational groups. The authors concluded that early-life education did not protect against dementia diseases through increased cortical thickness (brain reserve index) but that educational level was associated with better performance on cognitive tasks, which is more in favor of an active model.

Even if it seems reasonable that enrichment factors are most beneficial for the cognitive reserve when encountered at younger ages, it should be taken into account that when we reach adulthood most of the brain has been functionally and structurally specialized for a variety of environmental demands (Johnson, 2001). Therefore, considering the high correlations in cognitive/intellectual capacity from young age to old age, how modifiable the reserve capacity is over the life span should be investigated.

**What is required to affect the cognitive reserve?**

Cognitive challenges that can serve to produce broader effects on cognitive functioning would, of course, have important implications for the aging society. More knowledge is needed concerning what level, amount, frequency, and type of cognitive challenge is most effective in increasing the proposed reserve capacity. Similar questions, how cognitive challenges can exert more widespread influences on cognitive functioning, are today important questions in cognitive training programs. Herein, the term “transfer” is often used to describe the phenomenon when effects of training (or other experiences) are spread to other tasks and/or processes than those explicitly practiced (Barnett & Ceci, 2002).

So far, most cognitive training programs on humans have reported relatively domain specific and near transfer effects. This means that when transfer occurs, these are primarily restricted to highly similar situations (Detterman, 1993) referred to as “near transfer” (Sandberg, Rönnlund, Nyberg, & Stigsdotter Neely, 2014). In general, far transfer effects to other areas than those being practiced have been hard to demonstrate (Kalat, 2013). Most training studies, however, have the lack of long-term intense multi-modal training. A recent study by Schmiedek, Lövdén, and Lindenberger (2010) found, by using an intense training program (100
hours), that multi-modal training in episodic memory, perceptual speed, and working memory could generate transfer to untrained tasks. Thus, if similar results can be confirmed in future studies, cognitive training has the potential to provide new insights into how cognitive challenges can improve cognitive functioning and, in theory, how cognitive challenges can potentially influence cognitive reserve capacity.

More knowledge is also required about how generalizable the effects of transfer found in laboratory settings are to everyday life and vice versa. This would have practical implications for the aging society.

**Effects might differ depending on outcome**

Although it is possible that broader effects of cognitive stimulation may differ depending on when these occur during the lifespan, it might also be that effects differ depending on what outcome is measured. As previously noted, there is support for distinguishing normal aging from pathological aging. Dementia diseases are chronic and progressive disorders (Kurz & Lautenschlager, 2010) and are diseases for which there are no cures. Therefore, even if cognitive impairments can be postponed in pathological aging, the underlying factors that drive cognitive changes might be stronger than those causing changes in normal aging, and it is possible that effects might differ depending on the outcome of normal cognitive aging compared to pathological aging. Thus, even though beneficial long-term effects were found among the middle-aged for certain memory abilities in Study III, what relevance these might have for cognition and risk of dementia later in life remains an unanswered question. Furthermore, because the amount of variance in memory ability and change explained by social network size was still relatively small, caution should be taken not to draw any strong parallels between the effects found in Study III and risk of dementia in later life.

**Cognitive reserve or reverse causation?**

It should be noted that there are criticisms to the hypothesis that an active lifestyle is beneficial for cognitive functioning. Salthouse (2006) argues that there is little empirical evidence that cognitive aging is moderated by the amount of mentally stimulating activity. Salthouse argues that research often draws incorrect conclusions and that it is not at all certain that changes in activity level can predict cognitive capacity. He claims that it is important to consider that cognitive activity at any given age can be predicted by current and former cognitive capacity. According to Salthouse, much of what is assumed today is based on the desire to believe that cognitive exercise is beneficial for cognitive functioning.

Even if criticism has been raised towards the idea that cognitive stimulation might affect cognition, it should be noted that results from previous studies that have used other statistical methods in elderly
populations, have found that social participation (e.g., leisure and social activities) and social relations can predict future perceptual speed (Lövdén et al., 2005) and memory decline (Ertel et al., 2008) with less evidence of reverse causation. Thus, even if firm conclusions cannot not drawn in regard to directionality of the influence between social relationships and memory abilities in study III, it is plausible to believe that larger social networks might be beneficial for cognitive functioning from a long-term perspective.

In Studies I and II, however, the results might indicate a reverse relationship because effects were only found when near-onset participants were included in the analyses. The results of these studies are similar to previous studies that have used relatively short follow-up periods (maximum 5 years) after baseline measurement of both late-life mental and social activity (e.g., Akbaraly et al., 2009; Fabrigoule et al., 1995; Wilson et al., 2002a) and social relationships (e.g., Crooks et al., 2008; Helmer et al., 1999). Hence, there is the risk that previous studies were influenced by reverse causality. In Studies I and II, the number of participants decreased in the analyses after excluding those who became demented shortly after baseline. Even if the probability of a significant association decrease when reducing the number of participants from the analyses, the hazard ratios in both in Studies I and II also changed thereby indicating weaker associations.

Only a few studies investigating if leisure activity and social relations are protective against dementia in old age have controlled for the risk of reverse causality. These studies have, in contrast to Studies I and II, found beneficial effects. Wang et al. (2002) used a time period of three years between measurement of participation in leisure activities and first follow-up, in which participants were required to still be non-demented, and found that frequent participation in both mental and social-oriented activities were associated with decreased risk of dementia in old age (≥ 75 years). With a similar study design, Paillard-Borg et al (2009) found that higher factor scores on mental and social dimensions were associated with a lower risk of dementia. Regarding social relationships, Amieva et al. (2010) used a delayed entry of five years when investigating if certain aspects of social relations were associated with dementia in old age (≥ 65 years) and found that qualitative rather than quantitative aspects of social relations might serve to protect against dementia. Thus, despite the fact that many studies might have been influenced by reverse causality, there is support for the notion that the level of cognitive enrichment might predict the risk of dementia.

**Strengths**

Strengths of the studies included in this thesis must be highlighted. All of the studies included in this thesis involved longitudinal data with long follow-up periods. As can be seen from Studies I and II, results were modified
depending on follow-up period. To be able to carry out such analyses, longer follow-up periods are required. Furthermore, as can be seen in Study III, the results differed depending on cross-sectional or longitudinal analyses. Overall, as pointed out earlier, longitudinal data are essential for examining the relationship between enrichment factors and cognitive functioning. Furthermore, the studies also used data from a large randomized population-based sample, and in all studies the analyses were adjusted for a variety of potentially confounding factors. All these factors are key aspects if the intention is to make generalizations and to achieve credibility. However, several limitations must be considered.

**Limitations**

Although it seems reasonable to make certain interpretations about the directionality between variables used in the studies, associations between variables are the only thing that can be determined. To have something of substance to discuss regarding cause and effect, information about co-variation between variables over time is valuable. For example, in Study III, given the relatively few participants who contributed with longitudinal data over time regarding social network size, it was not possible to reliably analyze the co-variation between network size and cognition. Even if the use of longitudinal data facilitates the ability to examine predictions, we cannot, as discussed regarding probable reverse causality, truly determine the direction between variables. It might also be necessary to use a within-subjects technique to truly investigate whether or not changes in activity level can influence cognition.

Furthermore, most prominent in Studies I and II, measures of social relationships and leisure activity were used as the basis for analyses up to 16 years after baseline. Whether one measurement point in time is reliable when investigating social life and engagement in leisure activity as predictors of future risk of dementia must be discussed. It has been demonstrated, however, that lifestyle patterns are relatively stable. Mulder, Ranchor, Sanderman, Boumaa, and Heuvelac (1998) found that when including measures of smoking, alcohol consumption, physical activity, and dietary habits among men, almost 50% of the participants did not change their patterns in any of the domains over a period of four years. Among those who changed, 40% only changed in one lifestyle behavior, and only a small portion (11%) changed in two or more behaviors. Furthermore, we do not know if the participants continued to be active or not after baseline or had other changes in their personal lives. Unfortunately, it was not possible to investigate longitudinal changes in relation to dementia due the small number of participants who had repeated measures on leisure activity and social relationships.
In all three studies, composite measures were used as indexes. The main reason for this was the assumption that overall stimulation (i.e. the more the better), at least in theory, should generate more cognitive stimulation. We further labeled the composites as, for example, "mental activity", "social relationships", and "social network size", a method that is not straightforward. First, it is unlikely that these composites are mutually exclusive and only represent what they are supposed to measure. For example, items included, such as attending courses/workshops, is perhaps not only a social activity but is also a mental activity. In the same vein, indexes might represent dimensions not in the scope of this thesis. For example, the index of social relations used in Study II, including questions about satisfaction with contact frequency and having a close friend, might be very much related to other aspects than cognitive stimulation (this was the motivation to investigate each item separately in Study II). Although the desire was to conceptualize every composite used, there are always problems defining and operationalizing such concepts. In addition, the mix of questions, and the use of dichotomized and categorical data in composites, gives a rather coarse measure from a psychometric point of view.

It might be important to report the internal consistency of the composite measures that are used, as it was in Study I. The values for the indexes were low, especially for “mental activity.” It should be noted, however, that the choice of one leisure activity might decrease the time available to engage in other activities, and it is also not certain that individuals who are active in a so-called “social activity” automatically engage in other “social activities”. Cronbach’s alpha might therefore not be a fair index to evaluate reliability. It was decided to allow participants to subjectively categorize the activities as predominantly mental, social, or physical activities. However, the low Cronbach’s α, especially for the mental index, is of concern because it limits the ability to draw any firm conclusions about the association between the mental activity and dementia.

It is also possible that the activities and relations included in this thesis are not challenging enough cognitively to have any influence on the outcome variables used. Several of the factors, for example, reading magazines, watching movies and attending concerts, or just having a close friend say little about cognitive challenge. Including measures of cognitive demand and/or indicators of novelty seeking (interest in new activities or social relationships) might have altered the results. Unfortunately, we lacked information about how cognitively challenging the participants believed the factors were.

The issue of whether or not the effects of activities or social relationships are dependent on the type of dementia is a relevant question. Given that a sufficient number of cases, for instance, of vascular dementias were not available, in particular in the analyses where cases with short
survival were excluded, such analyses were not meaningful in the present study.

Finally, another important aspect that should be considered is the extent to which the Betula sample is representative of the target population. Nilsson et al. (1997) showed that the Betula sample has a good population validity with regard to several factors, including gender, marital status, employment, education, income, and number of persons in the household. Although the sample might be representative in terms of several demographic factors, it is still possible that those who chose to participate were more likely to have better health status compared with non-participants (see Drivsholm et al., 2006) resulting in a selection bias towards participants with a more active and socially integrated lifestyle that might have blurred potential associations.

**Implications and future directions**

Studies I and II have important implications in regard to methodology and show that future studies would benefit from using longer follow-ups and to adjust for reverse causality.

Regarding Study III, even if the variance explained by the social network was small, the results must be put into perspective of how robust our memory functions are over most of middle age, particularly in terms of episodic and semantic memory. Although strong conclusions cannot be drawn, the knowledge that social network size can have positive effects on cognitive performance has implications for the future. In an aging population, it might be important to know if interaction in larger social networks in midlife might have beneficial effects when entering old age.

Some important topics for future research have already been mentioned, such as the importance of examining co-variation over time in order to investigate the causal relationship between enrichment factors and cognition. It is also important to investigate how modifiable cognitive reserve is across the life span and what cognitive challenges are needed to affect the reserve. In addition to the shortcomings of the scales used in the present studies, there is an urgent need to find new methods to capture patterns of everyday life. Although this is not unproblematic, considering community development and how rapid technological and informational expansion are constantly opening up new alternate forms of leisure activities and social relationships (i.e. social media), an adjustment for this in the design of new instruments, to the extent that it is possible, is required.

As can be seen in reviews regarding, for instance, leisure activity (e.g., Fratiglioni et al., 2004; Stern & Munn, 2010; Wang et al., 2012), there are a variety of instruments used to measure individual patterns. Although more or less formal activity scales are sometimes used, such as the Adelaide Activities Profile (Clark & Bond, 1995), or the RIASEC activity list (Parslow
et al., 2006), these are, as are most other scales, based on a number of predetermined activities, and this might limit the possibility of capturing the broad spectrum of leisure activities available in today’s society. One possible way to solve this challenge is similar to that of Paillard-Borg et al (2009) who used an open-ended question method of measuring activity type and frequency of engagement. This is not only a relatively simple method, but it is also an approach that could be used in future studies to capture individual patterns. Although this can make it more problematic to manage the data, the open-ended question approach might be the best way to capture the wide range of activities and social networks that people engage in today. Diary studies might also be a reliable way to capture everyday life in regard to leisure activities. In addition, future studies will have to provide measures that capture all possible forms of activities and social relationships that the digitally networked world allows.

Most previous research on cognitive aging has focused on deficits that often come with aging and on differences between normal and pathological aging. Little attention has been paid to those individuals who actually show little or no cognitive decline. Data from the Betula Project (Nilsson et al., 1997, 2004) show that about 10% of the participants over 70 years are still relatively stable in performance and do not indicate any signs of decline. Nyberg et al. (2012) discuss a complementary concept to the cognitive reserve, referred to as brain maintenance, and they highlight that some elderly have a relative lack of brain pathology and have well-preserved memory function. Furthermore, when comparing younger adults and high-performing older adults, the activation pattern between them is often similar. More studies should be directed toward those who maintain neurochemical, structural, and functional brain integrity in old age.

As evidenced in Studies I and II, the integration of several other disciplines in the research of memory, including psychiatry, genetics, and epidemiology, not only makes it possible to obtain a more complete picture of the cognitive aging process, it also provides greater understanding of individual differences. The development of brain imaging techniques such as position emission tomography and functional magnetic resonance imaging provide opportunities to longitudinally investigate how changes in structure and brain activity affect cognitive functioning. In addition, such methods also provide possibilities to investigate individual changes, what characterizes those changes that preserve cognitive functioning in old age, and how such differences are influenced by environmental factors. Sophisticated neuroimaging methods might also be useful as diagnostic tools to identify early signs of pathological disease progression and might be helpful for developing pharmacological and/or cognitive treatments in the future.
Future interventions, including intense multi-modal training programs together with brain imaging techniques, might allow for a deeper understanding of parameters associated with changes in brain structure and function. Refined methods might also give the opportunity to investigate the cognitive reserve more closely because little is currently known about the architectural neural basis of the reserve (Esiri & Chance, 2012). Thus, investigating how individuals with similar brain pathologies process cognitive information differently depending on different cognitive reserve indicators might give new insights into the reserve concept. Thus, future interventions and cognitive training programs should be integrated with imaging techniques in order to investigate whether or not changes in lifestyle activities can cause changes in structure and function (and thus in performance) and thereby have positive effects on everyday functioning.

Finally, as shown in Studies I and II, genetics is an important aspect of cognitive aging. Identification of additional genetic factors, and further knowledge of how environmental factors might influence our individual genetic characteristics and cognitive progress, should enhance the understanding of how to postpone cognitive decline and dementia.

Conclusions
Results of the studies included in this thesis suggest that cognitive stimulation in middle age (40-60 years), such as having a large social network, has beneficial effects on cognitive functioning. Enrichment factors measured in old age (≥ 65 years), however, such as engagement in leisure activities or having a number of social relations, did not alter the risk of all-cause dementia or AD when near-onset dementias were removed from the analyses. Such results highlight the importance of having a long follow-up period and adjusting for reverse causality when investigating the impact of an active lifestyle among the elderly. Even if the results showed that age, gender, and genes are of significance for an increased risk of dementia and/or AD, finding evidence for factors that can be influenced by changes in behavior, such as other aspects related to leisure activity and social relationships, are of future interest. More studies are needed that 1) include measures of cognitive stimulation over the entire life-span, 2) that use refined instruments that capture a broader spectrum of everyday life, and 3) that integrate other research disciplines such as neuroimaging. Future studies should also identify factors that characterize brain maintenance and that examine potential interactions between genes and the environment in order to investigate the influence of cognitive stimulation as a way to postpone dementia diseases.
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