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The importance of social relationships in the process of cognitive ageing

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General discussion



INTRODUCTION

Late-life cognitive impairment and dementia are considered a major public health concern because of high prevalence rates and high economic and social burden¹. Currently, no curative treatments for dementia are available². Therefore, prevention is a key element to counteract the dementia epidemic^{3,4}. Increases in life expectancies worldwide will lead to an absolute increase in the number of people with dementia in the coming years. In 2015, more than 46 million people worldwide were affected by dementia and this is expected to increase to 131 million by 2050⁵. However, better education and economic well-being in combination with better control of vascular and lifestyle risk factors may result in lower age-specific prevalence rates of late-life dementia than initially predicted⁶. Poor social functioning is recognized as modifiable risk factor for the development of dementia. However, in general it receives less attention than the well-known risk factors of dementia, such as education level and vascular risk factors. This thesis focusses on poor social functioning as risk factor for cognitive decline and dementia. The overall aim is to evaluate which aspects of social functioning are related to which specific stages of cognitive decline. A broad range of social functioning aspects are taken into account. In this thesis, two commonly distinguished aspects of social functioning⁷⁻¹⁰ are specifically investigated, including : 1) the structure of the social network, such as the size and the frequency of contact between the members of the social network, and 2) the function of the social network, such as the perceived amount or quality of social support received from the network.

The present chapter provides a summary of the main research findings, a discussion of the association between social functioning and various stages of cognitive decline, a discussion of methodological considerations, and implications for future research.

MAIN FINDINGS

Various social functioning aspects seem to be related to different stages of cognitive decline (see Figure 1). To assess the relationship between social functioning and cognition among people from the general population, we conducted two meta-analyses focusing on the association between social relationships and incident dementia and the association between social relationships and cognitive decline. We found that social relationships that represent the lack of social interaction (i.e. low social participation, less frequent social contact, and more loneliness) were associated with incident dementia (**Chapter 2**). Regarding cognitive decline, we found that multiple aspects of social relationships (i.e. structural and functional aspects, as well as the combination of both) were associated with cognitive decline. However, the results of this meta-

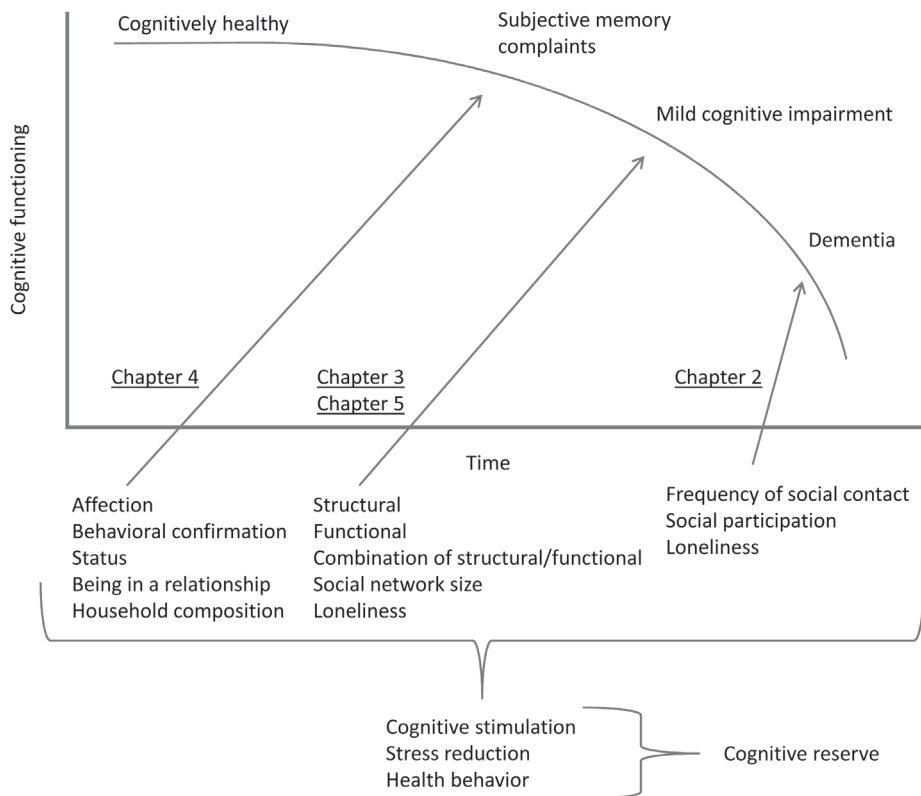


Figure 1. Effect of social functioning on subjective memory complaints, mild cognitive impairment, and dementia.

analysis (**Chapter 3**) should be interpreted with caution due to the heterogeneity (i.e. differences in study design and measurements) between the studies included in the meta-analysis and because we cannot exclude residual confounding (i.e. the effect of and unmeasured factor) and/or reverse causation (i.e. incipient decline affecting the seeking of cognitive stimulation)¹¹. Further, data from two observational studies were used to answer questions concerning the association between social functioning and subjective memory complaints (SMC), as well as whether social functioning relates to cognitive decline among a specific sample of depressed older persons. Results showed that both structural (i.e. being in a relationship, living in a larger household composition) and functional (i.e. better feelings of affection, behavioral confirmation, and status) aspects of social functioning were associated with SMC (**Chapter 4**). Whereas among older adults with a diagnosis of depression neither structural (i.e. social network size), nor functional (i.e. loneliness) aspects of social functioning were associated with cognitive decline (**Chapter 5**).

COGNITIVE FUNCTIONING; COURSE OVER TIME

Some decline in cognitive function is considered part of normal ageing, although there are great individual differences in the rate and timing of cognitive decline¹². Accelerated cognitive decline and a deviation from population norms based on age and education level can be defined as cognitive impairment, with a classification of mild cognitive impairment (MCI) or dementia as result. The development of dementia is generally a slow process which starts long before symptoms are detectable¹³. Three stages of cognitive decline in the progression to dementia can be classified, starting with a preclinical phase during which subjective memory complaints (SMC) may develop, followed by mild cognitive impairments (MCI), and subsequently a diagnosis of dementia¹⁴.

Dementia is a neurodegenerative disease characterized by a significant decline in cognitive functioning which interferes with independence in everyday activities¹⁵. Alzheimer's disease (AD) is the most common cause of dementia worldwide¹⁶. AD has a gradual onset and memory impairments are a core symptom of the disease¹.

The term *MCI* was introduced to describe patients at the intermediate stage between normal ageing and dementia¹⁷. The main difference between dementia and MCI is whether or not there is significant interference in independence in everyday activities¹⁵.

SMC are often one of the first symptoms of cognitive decline¹⁸ and are included in the criteria to diagnose MCI¹⁹. The stage of SMC is suggested to last many years before MCI occurs and the further development of dementia²⁰. However, it should be kept in mind that SMC can also be associated with conditions other than the progression of dementia²⁰, such as demographic variables (i.e. older age, female sex, lower education level)^{21,22}, depression²¹⁻²³, neuroticism^{23,24}, less exercise²², and multimorbidity²⁵. Particular attention should be paid to the potential presence of depression, as depression is one of the strongest predictors of SMC²¹⁻²³.

FUNCTIONS OF SOCIAL RELATIONSHIPS

Different aspects of social functioning may serve different functions in the protection against late-life cognitive impairments. This may explain why multiple aspects of social functioning are related to cognitive decline in different stages. Three functions of social relationships are considered; *cognitive stimulation, stress reduction, and enhancement of healthy behavior*.

First, the 'use it or lose it' theory suggests that the brain can be seen as a muscle and that engagement in intellectual, social and physical activities stimulates the brain²⁶. For example, recent evidence from a cognitively stimulating intervention study suggests that engagement in a three-dimensional multitasking video game (NeuroRacer)

contributes to the enhancement of cognitive abilities²⁷. Disengagement in everyday activities may result in disuse of the brain which in turn relates to decline of cognitive functions²⁶. Being in a relationship, living in a larger household (**Chapter 4**), having more frequent social contact, more social participation (**Chapter 2**), and the combination of good structural and functional aspects of social relationships (**Chapter 3**) may all contribute to a more stimulation environment and stimulation of the brain (*cognitive stimulation*).

Second, the *stress-buffering hypothesis* suggests that social relationships are beneficial in stressful situations⁹. Stress has been associated with cognitive decline and the development of AD due to structural changes in the hippocampus^{28,29}. Social relationships may prevent or modulate responses to stressful events that are damaging to the brain⁹. Better feelings of affection, behavioral confirmation, and status (**Chapter 4**), lower feelings of loneliness (**Chapter 2 and 5**), and the functional aspects of social relationships (**Chapter 3**) may all function as stress-relievers (*stress reduction*).

Third, the *main-effect hypothesis* suggests that social relationships have a protective effect on health through several pathways⁹. General normative guidance about health-behaviours obtained from the social network may influence health by motivating positive health behavior, such as physical activity and non-smoking⁹. Additionally, integration in a social network may directly produce a positive psychological state, which may also increase motivation for positive health behavior. Social resources may yield multiple sources of information that can help to make effective use of the available health institutions. This may for example help increase regular exercise, or moderate alcohol intake⁹. These positive health behaviors such as physical activity and non-smoking are shown to have a beneficial effect on cognitive functioning^{30,31}. A positive psychological state may modulate the neuroendocrine response to stress, which affects the brain^{9,29}. Being in a relationship, living in a larger household (**Chapter 4**), more social participation (**Chapter 2**), having a larger social network (**Chapter 5**), and the structural aspects of social relationships (**Chapter 3**) may all contribute to better integration in a social network, which may lead to better health behaviors and thereby reducing the risk of cognitive decline (*enhancement of healthy behavior*).

All three functions of social relationships may contribute to building cognitive reserve throughout life (see Figure 1). The *cognitive reserve theory* suggests that stimulating environments can build resilience to cognitive ageing and that social interaction affects brain structure and results in more efficient use of brain networks³². Mental and physical stimulation early in and throughout the life course is believed to increase cognitive reserve and help maintain cognitive function in old age, and thereby delay the onset of dementia². The construct of cognitive reserve can thus explain differences in the rate of cognitive decline and the clinical manifestation of dementia between individuals faced by neurodegenerative changes that are otherwise similar in nature and extent^{2,32}. Based

on the results described in this thesis, we found evidence that various social functioning aspects are associated to all three stage of cognitive decline. Although it is still unclear which mechanisms underlie the associations between social functioning and cognitive decline, the results may indicate that various social functioning aspects may contribute to the cognitive reserve through these three functions of social relationships (cognitive stimulation, stress reduction, and enhancement of health behavior). However, this should be investigated in more detail in longitudinal studies using a life course approach. The question remains whether there is an optimal “window of opportunity” to apply certain prevention strategies for the prevention of cognitive decline and dementia. Unfortunately, the results of this thesis do not permit to make firm statements about whether specific social functioning aspects have a different contribution to the different stages of cognitive decline.

LEVELS OF PREVENTION

Recently, the World Health Organization and the G8 Dementia Summit have highlighted prevention as one of the key elements in managing the dementia epidemic⁴. An average delay of two years in onset of AD could decrease the world-wide prevalence of AD by 22.8 million cases by the year 2050 which would considerably alleviate social and economic burdens³³. Most studies to date focused on the prevention of dementia. However, possibly more could be gained by prevention of milder forms of cognitive impairment, before too much neural damage is done³⁴. Prevention strategies can be divided into three stages, each aimed at a different stage of the disease³⁴ (see Figure 2).

The goal of *primary prevention* is to reduce the incidence of disease by preventing the occurrence of specific risk factors through health promotion and maintenance of good health³⁴. Higher levels of educational attainment with additional cognitive stimulating occupational attainment and leisure activities contribute to building cognitive reserve during childhood and middle life². A rich social network may offer opportunities for cognitively stimulating activities, reduction of stress, and enhancement of health behavior during this time frame^{9,35}. Results from the present thesis showed that better feelings of affection and behavioral confirmation were associated with lower risk of developing SMC among older persons from the general population (**Chapter 4**). This would suggest that primary prevention, in a stage in which no cognitive symptoms are present, could be effective. Although lifestyle interventions are considered beneficial for all individuals, particular attention should be paid to disadvantaged children and young adults, and those from minority groups because of fewer opportunities due to lower socioeconomic status².

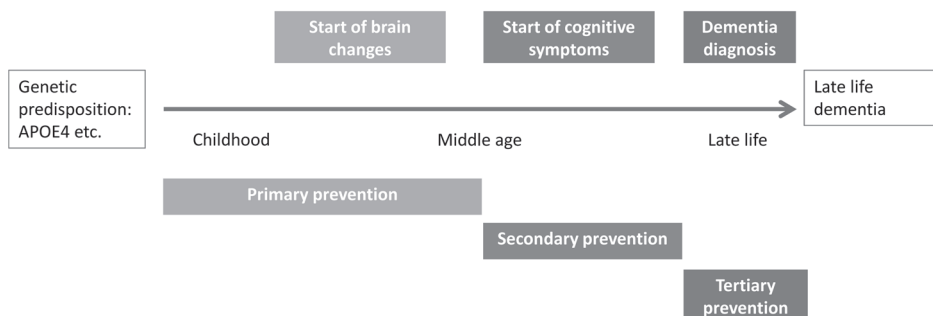


Figure 2. Levels of prevention of cognitive decline.

The goal of *secondary prevention* is to prevent cognitive decline at the very early and preclinical phase from progressing to more severe stages³⁴. During middle age and late life it is important to maintain and complement your social network in order to experience social interaction. Social interaction may stimulate cognitive functioning²⁶, reduce stress⁹ and may offer opportunities to adopt a more healthy behavior⁹. Multiple aspects of social functioning were found in the present thesis to be associated with the development of MCI and dementia (**Chapters 2 and 3**). Secondary prevention may be beneficial in the delay of mild (objective) cognitive decline³⁴. Although secondary prevention is considered to benefit all individuals during middle age and late life, especially those living alone or with a limited social network could benefit from this². Important changes in family and work trajectories can affect the composition of the social network³⁶. For instance, the loss of a spouse and the transition from working life to retirement are major life events which may have great impact on the social network^{37,38}. Although these are typical life events that may result in the loss of members from the network, this does not necessarily lead to a decline in social network size, as lost relationships are often replaced by new ones^{36,38}. Studies show that with increasing age, older people tend to report a stable social network size, including less contact with friends, but relatively stable or increasing levels of contact with close relatives^{36,39}. In addition, the amount of instrumental support received is shown to increase as people age^{36,39}. Furthermore, physical impairments may limit the opportunities to participate in social activities due to a decline in mobility⁴⁰. Secondary prevention focused on older persons with late life depression may be particularly beneficial in the prevention of further progression to dementia. In contrast to our results based on the general and overall healthy population, social functioning was not associated to cognitive decline among depressed older persons (**Chapter 5**).

The goal of *tertiary prevention* is to manage the manifestation of dementia and its complications, and to maximize quality of life³⁴. Even though there is advanced neurodegeneration in this stage of the disease, it is shown that, although limited, social

stimulation may still improve cognitive functions among dementia patients⁴¹. Furthermore, most people with dementia are passive during the day, which can have negative effects on physical, mental and emotional wellbeing^{42,43}. Increasing social interaction may therefore also have beneficial effects on the quality of life of dementia patients⁴²⁻⁴⁴.

METHODOLOGICAL CONSIDERATIONS

Observational studies; reverse causation

In this thesis, we found that various social functioning aspects are associated with different stages of cognitive decline. This is in line with other studies on the association between social functioning and dementia⁴⁵, cognitive decline^{8,46}, and SMC⁴⁷. However, previous research also showed that a decline in cognitive functioning is associated with loss of relationships³⁸. Therefore, reverse causation (i.e. cognitive decline may not be the consequence but rather the cause of poor social relationships) is an important methodological consideration which should be considered in observational studies on social functioning as determinant for cognitive decline^{26,48,49}.

For example, in a previous study it was examined whether low levels of social engagement were associated with risk of incident dementia⁵⁰. The level of social engagement was assessed in midlife (on average 27.5 years before dementia diagnosis) and at late life (on average 4.6 years before dementia diagnosis)⁵⁰. Results showed that low social engagement in midlife was not associated with incident dementia. However, low social engagement in late life as well as a decline in social engagement from midlife to late life, were associated with incident dementia. These results suggest that levels of late life social engagement may already have been affected by the dementia process and may be a prodromal symptom of dementia, indicating possible reverse causation⁵⁰.

Given the early onset of cognitive decline at a population level, the long preclinical phase before symptoms of cognitive decline or dementia are noticeable and the likelihood of reverse causation, we suggest in the design of population based longitudinal cohort studies to select healthy participants from the general population and include a long follow-up period in which both cognitive and social functioning are regularly monitored over the life span. These studies are often hampered by study attrition (also due to ageing populations), and research funding (i.e. long term follow-up). However, various studies in the Netherlands achieved this goal. The Longitudinal Ageing Study Amsterdam (LASA) is one such example. The aim of LASA is to study the determinants, trajectories and consequences of physical, cognitive, emotional and social functioning in relation to ageing⁵¹. LASA is an ongoing study with a follow-up period of more than 20 years, with first measurements started in 1992. Another example is the LifeLines Cohort study. Lifelines is an ongoing prospective population based cohort study aimed

to examine a broad range of biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population⁵². All participants receive a number of questionnaires and a basic medical examination at baseline (starting in 2006) and are followed for many years with extensive standardized measurements⁵². With regard to the observational studies in the present thesis (**Chapters 4 and 5**) we have tried to minimize the effects of reverse causation by applying a longitudinal cohort design and by excluding participants with severe cognitive impairments at baseline. With regard to the meta-analyses in the present thesis (**Chapters 2 and 3**) we have tried to minimize the effects of reverse causation by only including longitudinal population based cohort studies (i.e. mainly healthy population) and by performing subgroup analyses based on high/unclear risk of bias versus low risk of bias regarding reverse causation (i.e. excluding patients with baseline cognitive impairments or dementia). However, this cannot fully exclude the risk of reverse causation.

Systematic reviews; heterogeneity and publication bias

One important limitation in conducting meta-analyses is the inevitability of combining data from cohort studies which differ with regard to methodological and clinical characteristics. In both meta-analyses (**Chapter 2 and 3**) we encountered differences between studies regarding study population (e.g. age, gender), outcome measurements, social functioning measurements, and methodological quality of included studies. These differences lead to substantial heterogeneity in a) the results for social network size in relation to incident dementia (**Chapter 2**); and b) the results for all three social functioning aspects (structural, functional, and the combination of structural and functional) in relation to cognitive decline (**Chapter 3**). However, the findings of the meta-analyses regarding the association between social participation, frequency of social contact, loneliness, and satisfaction with the social network with risk of incident dementia were not affected by heterogeneity (**Chapter 3**). This could partially be explained by less heterogeneity in both determinant and outcome measurements in the meta-analyses on dementia (**Chapter 2**). Dementia was much clearer operationalized as outcome measure compared to cognitive decline. Furthermore, in **Chapter 2** we were able to make clearer distinctions between social functioning aspects, as five clear aspects came forward from the results. This was less clear in **Chapter 3** where we distinguished only between broader (more heterogeneous) terms, such as structural and functional.

Another limitation is that meta-analyses, and especially meta-analyses of cohort studies, are prone to publication bias and bias due to selective reporting⁵³. We found indications for publication bias, suggesting that the strength of the associations might be smaller than reported (**Chapter 3**). Many large observational studies including

measurements of cognitive decline probably also included one or more measurements of social functioning. However, if the main focus was not to investigate the association between social relationships and cognitive decline, or if associations were non-significant or small, results may not always have been reported (i.e. publication bias). For the conduct of a systematic review it is important that all potential confounders are measured and that the associations are reported in a quantitative way. It is therefore important to make better use of existing data. It would be interesting to identify within existing large population based cohort studies with low risk of bias whether associations between social functioning and cognitive decline could be assessed. This would offer opportunities to investigate these associations with limited resources. In addition, prospective registration of observational studies could make researchers methodologically more aware about the consequences of selective publication and may improve the methods of the study design and quality of reporting⁵⁴, resulting in more studies reporting on these associations.

IMPLICATIONS AND FUTURE DIRECTIONS

Measurements of cognitive decline

Many different tools are available to measure cognitive functioning. Researchers should consider during the preparation phase of the study, which tools should be used to measure cognitive functioning. The choice of the measurement tool also depends on whether the aim is to measure change over time (i.e. cognitive decline) or cognitive functioning at a certain time point (i.e. diagnosis of MCI or dementia). Furthermore, we would recommend monitoring cognitive functioning over a long period, using cognitive measurement tools that are able to detect the three stages of cognitive decline (i.e. SMC, MCI, and dementia). For a clinical purpose, measurements tools with good diagnostic accuracy (i.e. sensitivity and specificity) would be recommendable⁵⁵. Whereas for a research purpose, the course of cognitive functioning over time could be more of interest. For this purpose, measurement tools with good responsiveness may be more interesting⁵⁵.

A common method to evaluate the presence of SMC is by asking whether one experiences memory complaints (options for response yes/no)⁵⁶. This is a cheap and efficient way to assess SMC in cohort studies. However, also more comprehensive multi-item questionnaires which provide more insight in the severity and the content of the memory complaints are available⁵⁷, such as questions posed in the structured psychiatric interview section of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX)⁵⁸, the short Comprehensive Assessment and Referral Evaluation (Short-CARE)⁵⁹, and the Memory Complaint Questionnaire (MAC-Q)⁶⁰.

In addition, numerous tests are available to measure objective cognitive functioning⁶¹. Some tests are specifically aimed to measure a particular domain of cognitive functioning such as memory, praxis, attention, or planning, whereas other tests aim to measure general cognition⁶¹. Commonly used screening tests for dementia and cognitive impairment that cover a wide range of cognitive functioning domains (i.e. memory, language, orientation, attention, visuospatial functioning)⁶² include the Mini Mental State Examination (MMSE)⁶³, the Montreal Cognitive Assessment (MoCa)⁶⁴, the Cambridge Cognitive Examination (CAMCOG)⁵⁸ (i.e. part of the CAMDEX, including the objective evaluation of a broad range of cognitive functions), and the Addenbrooke's Cognitive Examination (ACE). In **Chapter 5** of this thesis, three common cognitive tests are used (i.e. the STROOP colored-word test, and two subtasks of the Wechsler Adults Intelligence Scale) and in **Chapter 6** we compared the scores on the Ruff Figural Fluency Test (RFFT), a paper-and-pencil-test to the scores of the CogState, a computerized cognitive battery. Correlations between these cognition tests were significant but of weak to moderate strength. Therefore, we conclude that cognitive functioning measured by the RFFT does not measure the same components of cognitive functioning as six subtasks of the CogState. Particularly the determination of mild cognitive decline in the very early stages of dementia is difficult, because baseline cognitive abilities vary among healthy individuals, and decline may not always be reflected by scores on neuropsychological testing⁶⁵. It is unlikely that one neuropsychological test can be used for the diagnosis of dementia as well as the early detection of preclinical cognitive decline⁶¹. Longitudinal examination of cognitive functioning, by means of a neuropsychological test battery covering multiple cognitive domains, is therefore recommended. Computerized testing such as the CogState is a valid and reliable tool for measuring cognitive functioning and changes over time in the general population. As it is a less time- and labor intensive tool compared to many paper and pencil tests, it is very suitable tool for measuring cognitive functioning in large population based longitudinal cohort studies⁶⁶.

Measurements of social functioning

With regard to the choice of the social functioning measurement tool, we suggest that researchers and clinicians consider the different functions of social relationships in the protection of cognitive decline; cognitive stimulation, stress reduction, and enhancement of healthy behavior. For the purpose of cognitive stimulation, measurements of social engagement and social interaction could be considered²⁶. These could include, for example, the level of participation in social activities with friends, family or community members, but also the frequency of social contact, having a partner, and the size of the household one lives in. Having a larger social network and frequent engagement with others may offer cognitive stimulation through organization of you social network

and engaging in new and sometimes challenging social situations and activities⁶⁷. For the purpose of stress reduction, measurements of social support could be considered, such as instrumental and emotional support, levels of loneliness, and satisfaction with social relationships. Social support and lack of loneliness may work as a buffer against stress^{29,68-71} and thereby protect against cognitive decline. For the purpose of enhancements of healthy behavior, the composition of the social network could be considered. For example, measures of informational support, social network size, and complexity and diversity of the social network. These social resources may motivate health behaviors (e.g. regular exercise, moderate alcohol use, non-smoking) and yield multiple sources of information that can effectively help the use of available health services, which in turn could have a beneficial effect on cognitive functioning^{9,30,31}. Furthermore, a more complex and diverse social network (i.e. having different social roles such as spouse, child, sibling, parent, friend) may provide more access to different sources of social support and contribute to a more enriched environment⁴⁶. Moreover, a complex and diverse network may also contribute to cognitive stimulation as they demand switching between multiple contexts⁴⁶.

Studies investigating the association between social functioning and cognitive decline often use a composite score for the measurement of social functioning. For example, the study of Saczynski et al. (2006) examined the association between level of social engagement and incident dementia⁵⁰. In this study, the level of social engagement among adults in their midlife was based on an overall composite score of engagement, including measures of marital status, living arrangement, participation in social, political, or community groups, participation in social events with coworkers, and the existence of a confidant. This was also assessed in late life (i.e. after 23 year follow-up), with the only difference that the question on participation in social events with coworkers, was replaced by a question on number of face-to-face or telephone contacts with close friends per month. The authors used the same categorization of social engagement (ranging from low to high levels of social engagement) for both assessments. The disadvantage of operationalizing social functioning as a composite score is that it is unclear which specific aspect(s) of social functioning relates to incident dementia. Furthermore, levels social engagement in middle life may not be comparable to levels social engagement in late life.

In a life course approach, change in social relationships through different stages in life is more important. It is shown that not only cognitive functioning changes over time, but also social relationships change. It is suggested that, in general, the size of the network decreases as people age and that roles of the network members change. A decrease in social network size is mostly due to a decrease in personal and friendships networks⁷². Both the size of the personal network (i.e. a selected network of close and supportive family members and friends) and the friendship network generally

decrease throughout adulthood and old age, whereas the family network (e.g., siblings, parents, children, and spouse) remains more stable in size from adolescence to old age⁷². Besides the loss of social relationships, social relationships can also be gained during ageing³⁶. The development of social relationships among ageing people can be quite heterogeneous and the network size and composition may be unstable (i.e. lost relationships may be replaced by old and new ones)³⁶. As people age, there tends to be an increase in the amount of support received from the network and an increase in the number of “helpers” in the networks of older persons with poor health^{36,38}. As the family network generally provides the majority of informal support for older adults, and the family network generally remains stable over time (as opposed to a decline of the friendship network), the composition of the network of older persons may increasingly consist of family relationships^{36,38}. Therefore, in the selection of suitable social functioning measurement tools, some measures may be more relevant during specific periods in one’s life and different categories may apply for difference age groups. For example, what would be considered a small social network during middle life could be considered a medium or large social network in late life due to the composition of the social network and the needs of the individual.

In this thesis, specific attention was paid to the presence and severity of late life depression as potential confounder in the association between social functioning and cognitive decline (**Chapter 5**). Late-life depression is associated with poor social functioning⁷³ as well as lower cognitive performance⁷⁴ and may thereby confound population-based findings. Results from our study among a sample of depressed older persons showed that neither social network size nor loneliness was associated with cognitive decline. We conclude that social functioning does not seem to contribute to cognitive decline over and above the presence of a depressive disorder. Therefore, in the design of future population based studies on the association between social functioning and cognitive decline, control for the presence of a depressive disorder is important, as it may explain the relation between social and cognitive functioning.

Multi-domain interventions

It was estimated that that up to a third of dementia cases could be prevented through optimal regulation of modifiable risk factors including cardiovascular disease and educational level^{3,75}. Interventions among the general population would probably be most effective if various lifestyle factors simultaneously are addressed^{29,48}. For the design of future cognitive and social intervention trials attempting to delay cognitive decline and the onset of dementia, it is important to consider multi-domain interventions. In the last few years, more attention is paid to the effectiveness of multi-domain lifestyle interventions for preventing cognitive impairment and dementia^{16,76}.

For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), randomly assigned 1200 participants (aged 60-77 years from the general population) to either a 2 year multi-domain intervention group (i.e. diet, exercise, cognitive training, and vascular monitoring) or a control group¹⁶. Results showed that after the 2-year program a significant beneficial intervention effect was seen on global cognition indicated by a 25% higher neuropsychological test battery score in the intervention group compared to the control group. Furthermore, the risk for cognitive impairment was 31% higher in the control group compared to the intervention group¹⁶.

Active engagement in mental, physical, and social activities may postpone the onset of dementia, possibly by increasing cognitive reserve³⁵. Based on the promising findings from multi-domain interventions and the results from the present thesis, we recommend that social functioning is incorporated in a multi-domain intervention. Multiple intervention studies among older adults have shown that it is possible to reduce loneliness and increase social support and the development of new friendships⁷⁷. There are only a few studies that recently investigated interventions focusing on improving social relationships aiming to improve or maintain cognitive functioning⁷⁸. One study investigated a multiple intervention that also included a social intervention on improving social interaction between people. Results showed that participants in this intervention group showed an improvement on multiple domains of cognitive functioning⁷⁹. Another intervention study showed that although the aim may be to improve one lifestyle (i.e. physical activity), also other lifestyle aspects (social interaction) can be affected⁸⁰. The aim of this intervention study was to investigate whether a walking program (i.e. 90 minute walking program conducted in small groups of 6 persons, once a week for 12 weeks long) among participants aged 65 years and older was effective in preventing cognitive decline after three months compared to a control group⁸⁰. Participants in the control group received education lectures on food, nutrition, and oral care that were not directly related to the prevention of cognitive decline. Not only did the intervention group show an increase in motor function and in cognitive function, they also showed benefits on social interaction and quality of life⁸⁰. Therefore, in the design of future (multi-domain) intervention studies, it is important to be aware of potential interrelations between intervention domains.

These encouraging findings from recent intervention studies suggest that we can slow down, prevent or maybe even reverse the process of cognitive deterioration. However, age is still the most important known (non-modifiable) risk factor for dementia⁴, and the risk of developing the disease doubles every five years over age 65. Genetic predisposition is another non-modifiable risk factor⁴. For instance, it has been estimated that 15 to 20% of dementia is attributable to the APOE ϵ 4 allele⁴. Nonetheless, it might be interesting to examine preventative strategies in high-risk groups based on their genetic profile.

A socially active lifestyle only seems to have a small contribution in the prevention of cognitive decline. In order to successfully delay the onset dementia, interventions on all modifiable aspects might be necessary in order to achieve the best results. However, it is known that changing health behavior is difficult due to the complex interplay of individual, social and environmental factors. Furthermore, certain social factors may be undesirable or unethical to intervene in, such as marital status or household composition.

In addition, placebo effects may influence the results in lifestyle intervention programs. An effect known as the *Hawthorn effect* suggests that merely involvement in a study, results in an effect⁸¹. This was also found in a dementia trial comparing intensive follow-up with minimal follow-up⁸². In the FINGER study the control group received general health advise which may in itself have an effect on lifestyle and therefore on cognitive functioning. Moreover, the received attention and social interaction during the trial on itself may also result in better cognitive functioning.

SOCIETAL IMPLICATIONS, PUBLIC HEALTH

From a societal perspective, policy makers could encourage people to adopt a socially active lifestyle by improving physical and social environments. These environments should meet the needs of the citizens. For example, places for older people to meet could be created, such as local community centers, senior centers, and green spaces (parks) with enough places to sit and meet people. These places should be save and easily accessible for people of all ages. Persons themselves can prevent social isolation by keeping their support system strong and develop new friendships. It is important to stay socially active and learn new things throughout life. For instance through volunteering, joining a club or social group, meet with friends and relatives regularly, and taking group classes.

CONCLUDING REMARKS

This thesis illustrates that multiple aspects of social functioning (i.e. structural and functional) are associated with all three different stages of cognitive decline (i.e. SMC, MCI, and dementia). Therefore we recommend that more attention should be paid to social functioning aspects in future cohort and multi-domain intervention studies. It is still unclear which mechanisms underlie the associations between social functioning and cognitive decline. Therefore, when selecting tools to measure social functioning in future studies, different functions of social relationships should be considered.

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