General Introduction

General aim and outline of the thesis
GENERAL INTRODUCTION

Worldwide, since 1950 life expectancy has increased by 2.5 years per decade.\textsuperscript{1,2} This increase resulted from the interplay of advances in nutrition, education, sanitation and medicine.\textsuperscript{2} Unfortunately, in this longer life span additional years in good health are not guaranteed. The risk of (chronic) disease increases with age. In the older age groups, the prevalence of chronic diseases such as cancer, cardiovascular disease, diabetes mellitus, chronic kidney disease and dementia is highest. In addition, increasing age is often accompanied with multimorbidity.\textsuperscript{3} The burden of chronic diseases leads to dependence in daily life and disability.\textsuperscript{3,4} Worldwide, the leading cause of dependence and disability in the elderly is dementia.\textsuperscript{5,6}

The global prevalence of dementia is expected to increase from 46.8 million persons in 2015 to 74.7 million persons in 2030.\textsuperscript{7} At the same time, the global economic costs of dementia will rise per year. It is estimated to increase from US $818 billion in 2015 to $2 trillion in 2030.\textsuperscript{7,8} The burden of dementia includes psychological distress and the impact on quality of life for both patient and caregiver. For the above-mentioned reasons the World Health Organization (WHO) concluded in 2012 that dementia should be regarded as a global public health priority. The WHO recommended to conduct more research on prevention strategies for dementia because up till now there is still no treatment to cure or to alter the progressive course of dementia.\textsuperscript{9} However, before prevention strategies for dementia can be examined, it is necessary to gain understanding about the course of cognitive impairment and factors associated with reduced cognitive performance.

**Cognitive performance across life span**

Cognitive performance develops and changes throughout life (Figure 1).\textsuperscript{10} The development of gray and white matter volume in the brain is dependent on the intrauterine environment, placental function and maternal nutrition during pregnancy and continues until the adolescence.\textsuperscript{10-13} A smaller brain volume is associated with reduced late-life cognitive performance.\textsuperscript{10} Not only the development of the brain volume has influence on cognitive performance, but also environmental factors in childhood. A higher socioeconomic status and a higher educational level in childhood are associated with better cognitive performance.\textsuperscript{10,14} Eventually, the development of cognitive performance achieves its peak around the third decade of life, after which it gradually declines.\textsuperscript{10}

Recently, the observational Whitehall study found that cognitive impairment is already evident at the age of 45 years.\textsuperscript{15} Interestingly, it is even supposed that cognitive performance reduces from the third decade of life.\textsuperscript{10} Indeed, it is estimated that brain volume decreases by
0.22% per year between the age of 20 and 80 years with accelerated decline with increasing age.\textsuperscript{16} Neuropathological changes in the brain like amyloid β and neurofibrillary tangles that are supposed to cause cognitive impairment may developed several decades before the clinical expression of dementia.\textsuperscript{17} Many factors may contribute to these neuropathological changes like increasing age, genetic factors and vascular risk factors. Cerebral vascular and neurodegenerative pathologies might arise with increasing age.\textsuperscript{18,19} Genetic factors as APOE ε4 carriersonship are associated with neurodegenerative changes due to amyloid β and neurofibrillary tangles, and with vascular changes due to atherosclerosis.\textsuperscript{20} Vascular risk factors (e.g. hypertension, diabetes mellitus, hypercholesterolemia and smoking) cause cerebrovascular lesions like lacunar infarcts or white matter lesions.\textsuperscript{21-23} In addition, intracranial atherosclerosis induce cerebral hypoperfusion and stimulate neurodegenerative changes like deposition of amyloid β.\textsuperscript{24} Thus, research showed various factors are related to cognitive impairment. However, the underlying pathogenesis of most factors are to be unraveled.

\textbf{Figure 1.} Hypothesized model on development and changes of cognitive performance from Muller et al., 2014.\textsuperscript{10}

ICV, intracranial volume; GM, gray matter; WM, white matter.
Interestingly, vascular risk factors are the only modifiable factors in contrast to age and genetic factors, and possibly useful as prevention target for cognitive impairment. Therefore, in line with the recommendation of the WHO, more research is needed to investigate the association of cognitive performance with vascular risk factors and its treatment.

**Hypothesis in this thesis**

As cognitive impairment is already evident at relatively young age and neuropathological changes associated with cognitive impairment may also be present at that moment, it is possible that starting treatment of vascular risk factors in as early stage as possible will be effective as prevention of cognitive impairment. Therefore, it needs to be explored whether vascular risk factors are associated with cognitive performance at a young age to confirm the hypothesis that vascular risk factors may contribute to cognitive impairment in its earliest stage. However, research in young persons may lead to methodological challenges. Methods have to be sensitive enough to measure the vascular burden and the first changes in cognitive performance in young persons. This should be further explicated before the research on the association of cognitive performance with vascular risk factors across the adult life span can start. If vascular risk factors are associated with cognitive performance at a young age, then the research of treatment of vascular risk factors as prevention target for cognitive impairment can be further explored.

**The association of cognitive performance with vascular risk factors**

As described above, vascular risk factors contribute to neurodegenerative changes in the brain. Hypertension, hypercholesterolemia, diabetes mellitus and smoking cause micro- and macrovascular changes resulting in brain atrophic lesions.\(^{21-23}\) Intracranial atherosclerosis is accompanied by thickening of capillary basement membrane and endothelial cell degeneration resulting in reduced cerebral blood flow.\(^{22,23}\) Chronic hyperglycaemia in diabetes mellitus affects brain tissue through direct toxic effect on neurons by oxidative stress and accumulation of advanced glycation end-products (AGEs) resulting in production of amyloid β neuritic plaques and neurofibrillary tangles.\(^{22}\) A high cholesterol level leads to increased deposition of cerebral amyloid β plaques.\(^{25}\) Thus, vascular risk factors contribute to neurodegenerative changes via various biological pathways and are thereby suspected to induce cognitive impairment.

In the recent decades, several observational studies examined the association of cognitive performance with vascular risk factors. The first studies observed whether a single vascular risk factor was associated with cognitive performance. In 1922, Miles and Root observed that persons with diabetes mellitus performed worse on measures of memory and
information processing speed compared to persons without diabetes mellitus. Between 1970 and 1980, various studies observed a negative association of cognitive performance with midlife hypertension. Subsequently, several longitudinal studies followed showing the association of increased risk of dementia and cognitive impairment with hypertension, hypercholesterolemia, smoking and diabetes mellitus.

After 2000, diverse observational studies showed that the risk of dementia increased if persons had two or more vascular risk factors suggesting that vascular risk factors interact or aggregate with each other and lead to a cumulative risk of dementia. Knowing that vascular risk factors often occur together, in the same period in vascular medicine several risk models were developed to predict an individuals’ risk of future cardiovascular disease or stroke based on combination of vascular risk factors. Consequently, given that elderly people have an increased vascular risk by the presence of multiple risk factors, various observational studies supported the idea that a high vascular risk is associated with poor cognitive performance.

Notably, a limitation of these studies is that they investigated the association of cognitive performance with vascular risk factors in persons aged 50 years or older. However, vascular risk factors may contribute to the onset of neurodegenerative changes several decades prior to clinical expression of cognitive impairment. It is therefore likely that vascular risk factors are associated with cognitive performance from much younger age on. The question remains whether the association of cognitive performance with vascular risk factors is already present in early adulthood and whether this association is different for young persons compared to old persons.

Research in young persons

Little is known about the association of cognitive performance with vascular risk factors in young adulthood. It is suggested that cumulative burden of vascular risk factors from early adulthood is associated with worse cognitive performance in mid-life. However, the studies were limited by methods that were not sensitive enough to measure the vascular burden and changes in cognitive performance in young persons. As well, a longitudinal trial in young persons was difficult to perform because of high costs, ethical issues and research efforts. Thus, there are several challenges in exploring cognitive performance and vascular risk factors in young persons.

First, vascular burden in young persons can be underestimated because single vascular risk factors often are only marginally elevated. However, vascular risk factors often occur together and act via shared biological pathways that may result in vascular burden. This had led to the development of vascular risk scores as described above.
By considering vascular risk factors together in young persons, it may result in a clearly increased vascular risk. An overall vascular risk estimation like in a vascular risk score is a good reflection of vascular burden in young persons.

Second, change in cognitive performance over time is small in young persons which may be underestimated by practice effects due to repeating the cognitive function test. Therefore, it needs to have a cognitive function test that is sensitive enough to the first changes in cognitive performance in young persons. The earliest changes in cognitive performance occur in the domain of executive function. Executive function encompass a variety of high-order cognitive processes, such as planning, inhibition, cognitive flexibility, decision-making and self-monitoring, and is commonly assessed by fluency tests. The mainly used fluency tests for evaluating cognitive performance in older persons in clinical care are Trail-Making-Test (TMT) and Stroop Color Word Test (SCWT). However, the differences between the test scores were too small in the young age groups to detect any changes in cognitive performance. A good possibly fluency test is the Ruff Figural Fluency Test (RFFT) that is sensitive to changes in cognitive performance in both young and old persons because of its wide score range. However, up till now, it is not clear whether the RFFT is hindered by a practice effect when it is repeated after years. Therefore, it needs to be explored how the performance on the RFFT after repeated measurements during years can be interpreted, especially in young persons.

Third, a longitudinal trial in young persons may be hindered by several methodological challenges. Such a study requires a large sample and long follow-up to detect the small changes in cognitive performance over time in young persons. This will be accompanied by high costs and research effort. Therefore, it is understandable to explore the association of cognitive performance with vascular risk factors cross-sectional first. Subsequently, if this association is found in a cross-sectional study, then it is possible to confirm this in a longitudinal study allowing a definitive conclusion on a causal relationship. The next desired step will be to explore the effect of treatment of vascular risk factors on cognitive performance in a randomized controlled trial (RCT). However, a RCT evaluating this research question is hindered by another methodological issue based on ethical principles. The importance of vascular risk management to prevent cardiovascular disease is undisputed and, therefore, withholding or withdrawing treatment in young control subjects for a long period would be unethical. Therefore, a good possibly design is a large observational longitudinal study to investigate the effect of treatment of vascular risk factors on cognitive performance, especially in young persons.
**General Introduction**

*Does treatment of vascular risk factors prevent cognitive impairment?*

If it is shown that vascular risk factors are associated with cognitive performance in both young and old persons, then it could be hypothesized that treatment of vascular risk factors prevent cognitive impairment. In several countries a trend towards declining incidence of dementia is seen over the past decades. This temporal trend and parallel improvement in cardiovascular health over time might be attributed to the benefit of improvement vascular risk management.\(^{53,54}\) This suggest that earlier diagnosis and more effective treatment of stroke and heart disease might have contributed to a lower incidence of dementia.

However, up till now, various randomized-control trials (RCTs) have found inconsistent results about the effect of treatment of vascular risk factors on cognitive performance. From 1991, only the Syst-Eur trial suggested a protective effect of antihypertensive treatment on dementia in contrast to other trials.\(^ {55,56}\) Similarly, from 2000, intensified single treatment of diabetes mellitus or cholesterol lowering treatment had no effect on cognitive performance in other RCTs such as the ADVANCE study and the PROSPER trial.\(^ {56-58}\) A limitation of these studies is that the intervention was focused on only one single vascular risk factor and did not include treatment of other vascular risk factors. In addition, in these studies the treatment was started at the age of 60 years or older.\(^ {55-58}\) However, it could be argued that starting treatment in old age may be too late for effective prevention of cognitive impairment, as vascular risk factors may contribute to the onset of neurodegenerative changes several decades prior to clinical expression of cognitive impairment. In summary, it is still unknown whether treatment of all vascular risk factors together is associated with cognitive performance, especially in young persons.
GENERAL AIM AND OUTLINE OF THE THESIS

The WHO recommends more research to prevention strategies for dementia. Vascular risk factors may contribute to the neurodegenerative changes in the brain associated with cognitive impairment. As cognitive impairment is already evident at relatively young age and neuropathological changes also be present at that moment, it is possible that starting treatment of vascular risk factors in as early stage as possible might be effective as prevention of cognitive impairment. Therefore, the general aim of this thesis is to explore the association of cognitive performance with vascular risk factors and treatment of vascular risk factors across the adult life span. We explore this association in the prospective observational Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study. Details on this study have been published previously. In this study, we explore the association of cognitive performance with vascular risk factors cross-sectional and evaluate whether this association is different for young persons compared to old persons. Before we confirm this association in a longitudinal study, we evaluate the longitudinal performance on cognitive function test because of the methodological challenge of repeatedly measuring cognitive performance in young persons. If there is an association of cognitive performance with vascular risk factors, then we investigate whether cognitive performance is also associated with treatment of vascular risk factors.

In Chapter 2, we examine the association of cognitive performance with an overall vascular risk and explore this association in various age groups including both young and old persons.

In Chapter 3, we study whether the association of cognitive performance with vascular risk factors is different for young persons compared to old persons. We chose to investigate this with the single vascular risk factor type 2 diabetes mellitus.

In Chapter 4, we explore the longitudinal performance on the Ruff Figural Fluency Test (RFFT) by measuring the cognitive test three times during a follow-up period of six years.

In Chapter 5, we investigate the association of the change in cognitive performance with a treatable general vascular risk during a follow-up period of six years.

In Chapter 6, we examine the association of the change in cognitive performance with treatment of vascular risk factors by comparing the cognitive performance of persons with and without treatment of vascular risk factors during a follow-up period of six years.

In Chapter 7, we describe a summary and general discussion of the key findings of this thesis.
References


