Summary and General Discussion
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Worldwide, the prevalence of dementia is expected to increase to 75 million persons in 2030. Because, up till now, no curative treatment is available, the World Health Organisation (WHO) recommends to conduct more research on prevention strategies for dementia. Cardiovascular diseases and dementia share similar pathogenetic processes, such as atherosclerosis, causing by common vascular risk factors like hypertension, hypercholesterolemia, diabetes mellitus and smoking. Therefore, it is generally assumed that early treatment of vascular risk factors might be an effective strategy to prevent dementia.

However, various randomized-controlled trials have found inconsistent results about the effect of treatment of vascular risk factors on cognitive performance. A possible explanation for these results is that the treatment was initiated too late, as it was started at the age of 60 years or older. It could be argued that starting treatment at this 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 the clinical expression of cognitive impairment. Therefore, in line with the recommendation of the WHO, the general aim of this thesis was to explore the association of cognitive performance with vascular risk factors and its treatment during the whole adult life span. We explored this association in the prospective observational cohort of the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study comprising persons aged 35 to 82 years old.

We encountered several challenges in exploring cognitive performance and vascular risk factors in young and middle-aged persons. It is generally felt that previous studies exploring this association in this age group were limited by methods that were not sensitive enough to measure the changes in cognitive performance and vascular burden in young and middle-aged persons. Therefore, we searched for various solutions to these methodological issues. First, we chose to measure cognitive performance with the Ruff Figural Fluency Test (RFFT) in addition to a memory test, because it is sensitive to the earliest changes in cognitive performance in both young and old persons. Second, by using a well-validated vascular risk score like the Framingham Risk Score for Cardiovascular Disease, we explored the synergistic effects of vascular risk factors instead of focusing on a single risk factor. Moreover, vascular risk scores are particularly valuable to identify the vascular burden in young and middle-aged persons because in this age group vascular risk factors often are only marginally elevated if considered separately but result in a clearly vascular burden if considered together. However, although age is a major vascular risk factor, it is not amenable to treatment or prevention strategy. Therefore, we decided to
also explore the association of cognitive performance with treatable vascular risk factors independent of age. To this end, we used a treatable vascular risk score based on the treatable components of the Framingham Risk Score for Cardiovascular Disease. In the next section, we describe the main findings of the thesis.

**Summary of the main findings**

We explored the association of cognitive performance with vascular risk factors and its treatment stepwise. First, we examined the association in both young and old persons cross-sectionally. Chapter 2 showed that a worse overall vascular risk was associated with poor cognitive performance. This was not only found in the older age groups, but also in the young age groups of 35-54 years old. In Chapter 3, we explored whether this association was different for young persons compared to old persons. We evaluated this research question with the single vascular risk factor type 2 diabetes mellitus as we found in Chapter 2 that diabetes mellitus was one of the main influencing components of vascular risk. Chapter 3 showed that persons with type 2 diabetes mellitus had poorer cognitive performance than persons without diabetes mellitus. This confirmed the results of Chapter 2 that cognitive performance is negatively associated with vascular risk factors. Interestingly, Chapter 3 showed that the difference in cognitive performance between persons with and without diabetes mellitus was largest at age 35-44 years and gradually decreased with increasing age. Thus, the association of cognitive performance with diabetes mellitus was strongest in young persons.

Second, we further explored the association of cognitive performance with vascular risk factors longitudinally. Before evaluating this, it was necessary to evaluate the longitudinal performance on the Ruff Figural Fluency Test (RFFT) because, up till now, it was unknown how the RFFT score after repeated measurements could be interpreted. In the PREVEND study, the performance on the RFFT was measured three times over an average follow-up period of six years. Chapter 4 showed that the performance on the RFFT increased by repeated testing. This is in contrast with the expectation that cognitive performance declines with increasing age. So, repeating the RFFT causes a practice effect. In addition, the increase in performance on the RFFT was largest in young persons and gradually decreased with increasing age. The increase in performance on the RFFT was not dependent on educational level. Thus, in longitudinal designs we have to adjust the change in cognitive performance measured by the RFFT for a practice effect.

Accordingly, it could be investigated whether the change in cognitive performance was influenced by vascular risk as measured with the treatable vascular risk score. Chapter 5 showed that the change in cognitive performance was negatively associated with treatable
vascular risk in both young and old persons. This supported the hypothesis that treatment of vascular risk factors might be effective as prevention of cognitive performance.

Finally, in Chapter 6, we explored whether treatment of vascular risk factors could be useful in preventing cognitive impairment. We evaluated this by comparing the change in cognitive performance in persons with and without treatment of vascular risk factors during a follow-up period of six years. Treatment of vascular risk factors included pharmacological treatment of hypertension, hypercholesterolemia, diabetes mellitus and prevention of arterial thrombotic events. The change in cognitive performance did not differ between the persons with and without treatment of vascular risk factors despite the fact that at baseline the persons with treatment were older, had high treatable vascular risk and worse cognitive performance. In other words, we found no evidence that pharmacological treatment of vascular risk factors did improve the cognitive performance of persons with a high treatable vascular risk.

To summarize, this thesis described that vascular risk factors like hypertension, hypercholesterolemia, diabetes mellitus and smoking are associated with cognitive performance during the whole adult life span. The association of cognitive performance with vascular risk factors was strongest at young age. Therefore, it could be hypothesized that starting treatment of vascular risk factors in as early stage as possible might be effective as prevention of cognitive impairment. However, in this thesis we could not confirm this hypothesis as treatment of vascular risk factors did not improve nor worsen cognitive performance of young and old persons with a high treatable vascular risk during a period of six years.

General Discussion
This thesis underlines two important considerations for further research on prevention strategies for cognitive impairment. First, it should be considered to perform this research during the whole adult life span as vascular risk factors are associated with cognitive performance at a young age. However, this implicates several methodological issues in exploring the effect of a prevention strategy on cognitive performance. Second, it should be considered to start the prevention of cognitive impairment as early as possible and, therefore, in young persons. However, young persons are then exposed to longer duration of prevention and to possible adverse events. These two important considerations are discussed in the next sections.
Prevention research during the whole adult life span

In this thesis, we found that the changes in cognitive performance caused by vascular risk factors start at a relatively young age (Chapter 2 and 5). This confirmed the hypothesis of Muller et al. that cognitive performance gradually declines from the third decade of life and that vascular risk factors contribute to this process.\(^\text{15}\) As well, it supported the observation from the Whitehall study that cognitive impairment is already present at a relatively young age.\(^\text{16}\) Consequently, the prevalence of cognitive impairment increases from the fourth decade of life in the same way as the prevalence of other chronic diseases such as osteoarthritis, cardiovascular disease, diabetes mellitus and cancer.\(^\text{17,18}\) It is likely that the biological processes responsible for all these chronic diseases start several years prior to the clinical expression of the disease.\(^\text{19,20}\) Subsequently, it could be hypothesized that starting treatment to stop or alter these biological processes in as early stage as possible might be effective as prevention. Therefore, research on prevention strategies for chronic diseases like cognitive impairment should not only be done in old persons, but primarily in young persons.

Most interestingly, the association of cognitive performance with vascular risk factors was strongest in young persons (Chapter 3). There are several explanations for this finding. First, the onset of vascular risk factors may be years before the clinical diagnosis.\(^\text{19-21}\) It is likely that in this preclinical period, untreated chronic hyperglycemia or hypertension already causes important and irreversible changes in the brain. For example, the vascular risk factors cause cerebrovascular lesions and atherosclerosis inducing cerebral hypoperfusion.\(^\text{5,22}\) Second, both people with and without vascular risk factors undergo age-related neurodegenerative changes that are caused by other mechanisms such as, for example, oxidative stress, mitochondrial dysfunction, protein misfolding, alterations in synapse integrity and dendritic spine remodeling.\(^\text{23,24}\) In addition, cerebral atherosclerosis is also associated with aging.\(^\text{25}\) Therefore, it can be suggested that the association between cognitive performance and vascular risk factors is weaker at old age by the competitive accumulation of different age-related cerebrovascular and neurodegenerative changes. The hypothesis is further supported by the finding that vascular risk factors may have a different predictive value in young and old persons. Several studies found, for example, that the presence of hypertension in midlife is associated with elevated risk on dementia, but this association is less certain when hypertension occurs in late-life.\(^\text{26,27}\) Accordingly, the effect of vascular risk factors on brain structure and cognitive performance may change across the adult life span.

Therefore, it needs to be considered to investigate prevention strategies for cognitive impairment during the whole adult life span. However, this leads to methodological issues
in exploring the effect of treatment of vascular risk factors on cognitive performance as prevention strategy. The most important issues are the choice of the primary outcome and the sensitivity of common risk scores to measure vascular burden in young and middle-aged persons.

**Methodological issue: primary outcome**

An issue in the research on prevention strategies for dementia is the choice of the primary outcome. Prevention or delaying the onset of dementia is generally preferred as primary outcome in current dementia prevention trials because of its apparently unambiguous definition according to existing guidelines. However, it should be considered to change the aim of these trials in prevention of cognitive impairment. The decline in cognitive performance before the clinical diagnosis of dementia may already have a large impact on quality of life for both patient and caregiver. Therefore, it is clinically more relevant to prevent cognitive impairment. Moreover, by using dementia as a primary outcome, the follow-up period has to be long and the sample size large to detect differences in incident dementia when the prevention starts at a relatively young age. For example, Richard et al. calculated a required sample size of 15,000 subjects for a dementia prevention trial when starting an intervention at the age of 60-70 years. This does not appear to be feasible. Therefore, we recommend using the changes in cognitive performance as primary outcome in the research on prevention strategies for cognitive impairment to make these trials feasible and clinically relevant.

The changes in cognitive performance could be measured with cognitive function tests. However, these tests have to meet a number of criteria to measure the small changes in cognitive performance over time in young persons. They need to be sensitive enough to the earliest changes in cognitive performance in young persons. As well, repeating the cognitive function test might cause a practice effect resulting in an increase in test score. Therefore, the change in cognitive performance over time should be well interpreted. In this thesis, we used the figure fluency test RFFT because previous studies showed its sensitivity to the earliest changes in cognitive performance in both young and old persons. As a result, we found that cognitive performance declines at a relatively young age (Chapter 2, 3 and 5). To monitor the change in cognitive performance over time, it is common practice to repeat the RFFT. Repeating the RFFT leads to an increase in test score possibly due to a practice effect (Chapter 4). Practice effects can be ascribed to different factors such as familiarity with the test, memory of specific test items and learning test strategies. Interestingly, the practice effect of the RFFT persisted three to six years after the first measurement of
the RFFT (*Chapter 4*). This longstanding practice effect was also found in other cognitive function tests such as the Verbal Learning Test (VLT) and the Stroop Color-Word Test (SCWT). They were even detectable up to seven years after the first measurement of cognitive performance. Therefore, practice effects in cognitive function tests are most likely not avoidable and have to be accounted for in longitudinal designs.

Practice effects, or in other words learning, may be a reflection of cognitive performance. A frequent early sign of dementia is impairment of the cognitive domain memory and learning. Subsequently, an improvement in performance on a cognitive function test at repeated testing may be the result of learning and represent a stable course of cognitive performance. Similarly, a stable performance on a cognitive function test at repeated testing does most likely not reflect a stable course of cognitive performance but decline. Therefore, we think that practice effects are a valuable outcome to evaluate the changes in cognitive performance over time. However, in order to have an estimate of the variance in performance due to practice effects in a repeated measurement design we need more longitudinal data in healthy persons.

**Methodological issue: measurement of vascular risk factors**

An important issue in exploring the effect of treatment of vascular risk factors on cognitive performance is the measurement of vascular risk factors across the adult life span. 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 finally result in a clearly elevated vascular burden. In this thesis, we found by using a vascular risk score that young persons may have the same vascular burden as older persons (*Chapter 2*). Therefore, by considering the synergistic effect of vascular risk factors in a vascular risk score, it may reflect more accurately the vascular burden in both young and old persons.

Importantly, we have to realize that vascular risk scores are largely based on age. Although age is a major vascular risk factor, age is not amenable to treatment or prevention strategy. Therefore, we decided to explore the association of cognitive performance with vascular risk factors by using a treatable vascular risk. The treatable vascular risk was based on the treatable risk factors hypertension, hypercholesterolemia, diabetes mellitus and smoking, independently of age. In this thesis, we found that the change in cognitive performance was associated with treatable vascular risk (*Chapter 5*). This suggests that treatment of vascular risk factors might be effective as prevention of cognitive impairment. But this is still not at all of proof of efficacy.
Pharmacological treatment of vascular risk factors as prevention

So far, in this thesis, we found that vascular risk factors are associated with cognitive performance at a relatively young age and, therefore, treatment of vascular risk factors may have the most effect on cognitive performance if it is started at a young age (Chapter 2, 3 and 5). So, we decided to investigate in a large community-based cohort whether treatment of vascular risk factors could be effective as prevention for cognitive impairment. Interestingly, we found that during a follow-up period of six years the changes in cognitive performance was similar between the persons with and without treatment of vascular risk factors despite the fact that at baseline persons with treatment were older, had higher treatable vascular risk and worse cognitive performance (Chapter 6). This suggests that lowering the vascular risk with treatment of vascular risk factors does not improve the cognitive performance. However, we found also that treatment of vascular risk factors does not worsen cognitive performance in people with a high treatable vascular risk. This is in contrast with other observational studies that suggest, for example, that lowering blood pressure in older people might lead to cerebral hypoperfusion and thus to poorer cognitive performance. Therefore, our findings suggest that treatment of vascular risk factors does not improve cognitive performance, but it does also not worsen the cognitive performance.

It is generally acknowledged that observational studies may overestimate treatment effect as compared to (subsequent) RCTs on the same questions. When exploring the effect of treatment of vascular risk factors on cognitive performance with an RCT, there are several challenges to overcome. As described previously, such a RCT requires a large sample and long follow-up to detect significant differences in cognitive performance between the treatment and the control group when the treatment starts at the age of 30 years. Additionally, the importance of vascular risk management to prevent cardiovascular disease is undisputed and, therefore, withholding or withdrawing treatment in control subjects for a long period would be unethical. Consequently, it is in fact infeasible to perform an RCT exploring treatment of vascular risk factors as prevention for cognitive impairment in young persons. Therefore, we think that our large observational cohort study comprising young, middle-aged and old persons adds valuable insights to what is known from recent RCTs in old persons.

Furthermore, it is unclear whether pharmacological treatment of vascular risk factors is cost effective as prevention strategy for cognitive impairment. An intervention that delays cognitive impairment could reduce the impact of this disease on quality of life for patient and caregiver. However, the question is whether pharmacological treatment of vascular risk
factors is a good intervention to reduce the burden of cognitive impairment. Prevention of cognitive impairment with treatment of vascular risk factors is not only accompanied with high costs of drugs and doctor visits, but also with the daily effort of an individual to take drugs possibly from his third decade of life. In addition, the individuals are exposed for a long period of time to possible adverse effects of these drugs which may result in other chronic diseases such as, for example, hepatitis or pancreatitis. So, there are also disadvantages to the treatment of vascular risk factors as prevention of cognitive impairment. Therefore, future research on the underlying mechanisms of cognitive impairment is necessary to know whether there are other opportunities to prevent cognitive impairment.

**Future perspectives**

Although the WHO recommends to conduct more research on prevention strategies for cognitive impairment, we need to ask ourselves to what extent cognitive impairment can be prevented. The neurodegenerative changes in the brain related to cognitive impairment start at a relatively young age. Therefore, it is likely that prevention may have the most effect on cognitive performance if it is started at a young age. However, young persons are then exposed to longer duration of prevention and to possible adverse effects. In this thesis, we found that treatment of vascular risk factors did not improve nor worsen the cognitive performance of persons with a high vascular risk. If we weigh this against the costs and possible adverse events, it seems likely that pharmacological treatment of vascular risk factors is the first appropriate prevention strategy for cognitive impairment. Therefore, more research is needed to explore whether other risk factors of cognitive impairment can be useful as prevention target for cognitive impairment.

Other risk factors are increasing age and genetic factors that may contribute to the neuropathological changes related to cognitive impairment. Unfortunately, genetic factors are yet not modifiable factors and, therefore, not useful as prevention target for cognitive impairment. Consequently, age is maybe the only risk factor that can be used as prevention target for cognitive impairment. However, up till now, several age-related biological changes in the brain associated with cognitive impairment are not yet fully understood, such as, for example, shrinkage in brain volume, alteration in synapse integrity and dendritic remodeling. Therefore, future research on the underlying mechanisms of age-related cognitive impairment is necessary to know whether there are opportunities to prevent cognitive impairment.
References


