Chapter 8

General discussion

This thesis aimed to 1) further investigate whether blood pressure in older people is a risk factor for cardiovascular events and cognitive impairment; 2) study whether early markers of cardiac disease are related with cognitive impairment; and 3) to evaluate the feasibility of home blood pressure monitoring using smartphone-assisted technology, which might eventually assist to prevent cognitive impairment.

Main findings

The first part of this thesis consists of three studies that evaluated the association of blood pressure and blood pressure variability with cardiovascular events and cognitive function in older age. In **chapter 2**, we investigated the association of blood pressure with the risk of cardiovascular events. We found that the association of diastolic blood pressure with cardiovascular events in older people varied upon cardiovascular history: in participants without a history of cardiovascular disease, there was no association between diastolic blood pressure and cardiovascular events, whereas participants with a cardiovascular history showed a decreased risk of cardiovascular events with higher diastolic blood pressure. **Chapter 3** assessed the association between visit-to-visit blood pressure variability and cognitive function in older people. Visit-to-visit blood pressure variability has previously been related to cerebrovascular damage. We showed that higher visit-to-visit systolic and diastolic blood pressure variability, independent of average blood pressure, was associated with worse cognitive function. Furthermore, we found that higher blood pressure variability was related to lower hippocampal volume and higher risk of cortical infarcts and cerebral microbleeds. We hypothesized that blood pressure lowering medication might mediate the association of blood pressure variability with cognitive function, possibly through its previously found effect on blood pressure variability.(1) In **chapter 4**, we found that use of beta-blockers and inhibitors of the renin-angiotensin system was associated with higher systolic blood pressure variability. However, the association between blood pressure variability and cognitive impairment was not mediated by blood pressure lowering medication. This strengthens the finding that blood pressure variability, independent of blood pressure lowering medication, is associated with cognitive impairment.

The second part of this thesis consists of two studies that addressed the association between early markers of cardiac disease and cognitive function. In **chapter 5**, we presented an association of N-terminal pro-brain natriuretic peptide (NT-proBNP), a neurohormone that is commonly used in the diagnosis of clinical heart failure, with worse cognitive function and steeper cognitive decline. **Chapter 6** showed that participants with high but

within normal ranges levels of cardiac troponin T (cTnT), routinely used in the diagnosis of acute myocardial infarction, had worse cognitive function and steeper cognitive decline. These results were independent of cardiovascular diseases or risk factors. Furthermore, similar trends were found in participants with lower NT-proBNP levels below which might be indicative of clinical heart failure, suggesting that hs-cTnT is an independent predictor of cognitive impairment.

In the last part of this thesis, we introduced the innovative research technology iVitality, which comprises a website, a smartphone-based application and health sensors to measure health characteristics at home (**chapter 7**). In a proof of principle study including 151 people, we evaluated the feasibility of home blood pressure monitoring using iVitality during six months. We showed a high correlation between office and home blood pressure measurements. In addition, adherence of participants to perform blood pressure measurements was high. Furthermore, we found a significant decrease in home blood pressure when participants were referred to their general practitioner in case of a high blood pressure. We therefore concluded that smartphone-based technology is a reliable and promising method with good adherence. This provides a possibility for implementation in large-scale studies and can potentially contribute to blood pressure reduction, eventually helping to prevent cognitive impairment.

Discussion

Previous studies showed that the association between high diastolic blood pressure and increased risk of cardiovascular events attenuated with older age, and even reversed in the oldest old or biologically old.(2-7) Our finding that low blood pressure associates with a higher risk of cardiovascular events in people with previous cardiovascular disease further supports the hypothesis that in older people, biological or vascular age might be more important than calendar age per se. In this manner, low diastolic blood pressure, which is an important contributor of the perfusion pressure of an organ, might predispose to vascular hypoperfusion of vital organs, particularly in people who already suffer from increased arterial stiffness or obstruction.(8, 9) Besides average blood pressure, we showed that variability in sufficiently high blood pressure might be important in older people, especially concerning cognitive function.

Blood pressure variability may reflect a long-term hemodynamic instability in the systemic circulation that puts stress on the vascular endothelium.(10, 11) This hemodynamic

stress may lead to endothelial dysfunction and micro-vascular damage with consequent alterations in brain structure and function.(12) Furthermore, exaggerated fluctuations in systemic blood pressure could result in repeated episodes of cerebral hypoperfusion causing neuronal injury and cell death, particularly in vulnerable brain regions such as the hippocampus.(13) Blood pressure management in older people might therefore be more complicated then what current guidelines include. In addition, a conservative approach in the treatment of high blood pressure in older people might be appropriate, especially in those with a cardiovascular history. All this underlines the importance of an individualized approach in blood pressure management, in particular for older people.

Our findings that NT-proBNP and cTnT associate with worse cognitive function and decline, is in line with earlier studies which suggest a connection between cardiac function and brain structures. A possible explanation might be that higher NT-proBNP and cTnT levels indicate suboptimal left ventricular functioning with subsequent decreased cardiac output and cerebral hypoperfusion.(14) Cerebral hypoperfusion has previously been associated with a higher risk of dementia.(15) In line with this, earlier studies showed that patients with clinical heart failure have an increased risk of cognitive impairment, and that patients following cardiac transplantation showed an improvement in cognitive function.(16-20) Nevertheless, the finding that in participants with NT-proBNP levels within the normal range and below those indicative of clinical heart failure, cTnT was also associated with worse cognition, merits further speculations on underlying pathways. Although it is generally believed that cTnT is only expressed in striated muscle cells, animal studies have revealed expression of troponin proteins, including troponin T, in smooth muscle cells of rats and mice as well.(21, 22) This suggest that cTnT might also be a reflection of smooth muscle cell involvement.(23) Higher levels of cTnT may therefore indicate vascular smooth muscle cell damage in an early stage, before the manifestation of clinical or even subclinical diseases. This might also explain the observation that higher levels of cTnT are associated with subclinical brain disease, including silent brain infarcts and white matter hyperintensities.(24) Speculatively, cTnT is not only released by cardiomyocytes but also by smooth muscle cells in the brain vasculature, and may therefore mark structural brain damage as a cause of cognitive decline. These findings emphasize that people with early signs of cardiac or vascular disease are already at increased risk of cognitive impairment. Furthermore, it supports the importance of early recognition and treatment of cardiovascular risk factors in the prevention of cognitive decline.

The findings of this thesis strengthen the potential to prevent cognitive decline by early control of modifiable risk factors, including blood pressure, blood pressure variability and

cardiac or vascular disease. Since treatment of early stages of cognitive impairment or dementia is still lacking, prevention is currently the only option to diminish the burden of these disorders. Recently, it has been shown that elevated blood pressure as measured in the home situation is a stronger prognostic indicator of cardiovascular events than elevated office blood pressure.(25-27) In view of the cost-effectiveness, the low burden of measuring, and manifold established treatment options, home blood pressure monitoring could therefore be an important strategy to further prevent cardiovascular complications, including cognitive disorders and dementia.(28) The evidence of the last part of this thesis, in which we showed that smartphone-assisted technology is a reliable and promising method with good adherence to measure blood pressure at home, offers new opportunities.

Future perspectives

The work described in this thesis tried to provide new insights in the relation of blood pressure and cardiac function with cognitive impairment. Most of the data in this study were obtained from the PROspective Study of Pravastatin in the Elderly at Risk, a randomized, double blind, placebo controlled trial with a mean follow-up period of 3.2 years. The longitudinal nature of this study provided the opportunity to study relations between (changes in) determinants and subsequent changes in cognitive function. However, a limitation of the design used in our studies, is the observational nature, which does not allow to make conclusions about causality.

As for the association between diastolic blood pressure and cardiovascular events, it could be that both low diastolic blood pressure and cardiovascular events share a common cause, which most likely would be aging of the arterial system, including atherosclerosis. Previous studies showed that progression of atherosclerosis is accompanied by a decrease in diastolic blood pressure.(29, 30) Instead of being causally related, low diastolic blood pressure might therefore be a reflection of widespread atherosclerosis, which itself associates with increased risk of cardiovascular disease and mortality. Another possibility might be that low diastolic blood pressure is a reflection of deteriorating health status, leading to increased risk of cardiovascular events and mortality.(31) So far, only one randomized controlled trial investigated whether older people benefit from higher blood pressure values. The Discontinuation of Antihypertensive Treatment in Elderly People (DANTE) study examined whether discontinuation of antihypertensive medication in patients aged 75 years or older decreased the risk of cognitive decline.(32) In 385 participants with mild cognitive deficits, they found no differences in cognitive, psychological or general daily functioning during a 16-week follow-up period.(32) However, the short follow-up and the (unintentionally)

selection of participants with relatively intact cerebral autoregulation might explain the lack of effect of the discontinuation of antihypertensive medication. Future randomized controlled trials should include longer follow-up and biologically older people with impaired autoregulation. Furthermore, although most trials study the effect of medication, the focus of research in older people should be whether discontinuation of medication results in better outcomes.

Doubts on the causal nature also holds for the relation between blood pressure variability and cognitive impairment: both could stem from a common cause, for instance cardiovascular risk factors, without themselves being related. In line with this, previous literature showed that cardiovascular and cerebrovascular disease share the same risk factors, including hypertension, diabetes mellitus and smoking.(16, 20) In addition, increased levels of cTnT and NT-proBNP might reflect underlying myocardial damage caused by cardiovascular risk factors, which themselves also cause cognitive decline.(16, 17) Therefore, randomized controlled trials could help to draw conclusions about causality and interventions to prevent cerebral damage. These trials should examine whether lowering blood pressure variability, for example by calcium-channel blockers, an effective drug-class in lowering blood pressure variability, diminishes the risk of cognitive impairment. Furthermore, to unravel biological mechanisms concerning cerebral autoregulation, future investigations should examine the role of blood pressure variability, NT-proBNP and cTnT with respect to perfusion, volumes and small vessel disease of the brain.

Finally, we showed the feasibility of home blood pressure measurements using smartphone-assisted technology during six months of follow-up. Results of this study are promising in light of an alternative research method to study relevant health characteristics at home. Besides blood pressure, new technologies allow home-based measurement of other lifestyle characteristics, such as physical activity, blood glucose concentration, gait speed and sleep parameters. Furthermore, this also provides interesting opportunities for implementation in prevention programs, in particular in a primary care setting. In addition, engaging people to measure their own health could further stimulate awareness and involvement. This might contribute to a more home-based, self-management approach, which is a welcoming alternative for the current hospital centered paradigm. Future studies should therefore investigate the potential of smartphone-assisted technology to prevent or manage cardiovascular risk factors and whether this results in less events. Eventually, this might lead to a reduction of cardiovascular diseases and may help in the prevention of cognitive decline.

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