# Keeping the heart in mind: Cardiovascular determinants of neurocognitive functioning in old age

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# Chapter 7

General discussion

## Scope

Cardiovascular risk factors and diseases are considered important determinants of late-life cognitive dysfunction[1], depression[2], and apathy[3]. In this thesis, cardiovascular factors indeed appeared to be important for neurocognitive functioning. Moreover, we found that apathy, depression, and cognitive dysfunction have distinct risk factor profiles in older persons. More specifically, in **chapter 3** we found that high sensitivity troponin T (hs-cTnT) was associated with cognitive dysfunction but not with apathy, and not consistently with depression. Further, lower late-life blood pressure was consistently related to apathy in older persons with lower functional ability (**chapter 4**) and with a higher burden of cerebral small vessel disease (CSVD, **chapter 5** and **6**), but we found no such pattern for depressive symptoms nor for cognitive dysfunction. Our finding that cardiovascular factors have different associations with apathy than with depression or cognitive dysfunction, supports the concept that while these syndromes may overlap in some patients, they can also be regarded as distinct clinical entities in older persons.

## Measuring apathy in research settings: the importance of the instrument used

As others have shown before us and we again have demonstrated in this thesis, apathy is an important yet often overlooked neurocognitive syndrome. Since depressive symptoms are often measured with the Geriatric Depression Scale (GDS)-15 in studies on older persons, a sub set of this scale, the GDS-3A (the three apathy items of the GDS-15), is increasingly being used to measure symptoms of apathy[3-5]. In **chapter 2**, we investigated scale properties of the GDS-3A compared to the Apathy Scale, to be able to appraise the use of this scale in research settings, including our own work. In both the PROMODE and DANTE Study Leiden, the GDS-3A showed a low sensitivity and high specificity and only moderately discriminates between presence and absence of clinically relevant apathy as measured with the Apathy Scale. Thus, one might argue that in case of no alternative the GDS-3A is an adequate enough substitute for measuring apathy in older observational studies. However, its limitations have to be taken into account when interpreting the research findings.

Because of the low discriminatory value, misclassification of the outcome measure is likely when using the GDS-3A. If this misclassification is non differential, it can be assumed that the resulting estimate will be biased towards the null[6]. Thus, studies with larger numbers of participants are more likely to have enough power to determine risk factors for apathy. In this thesis, we used the GDS-3A as

a measure of outcome in two different study populations. In **chapter 3**, we used the GDS-3A to investigate the association between hs-c-TnT and apathy in the Leiden 85-plus Study and in **chapter 6** we used it as an outcome measure for the association between blood pressure and apathy in the AGES-Reykjavik Study. It can be assumed in these studies that the misclassification of apathy did not depend on the level of hs-cTnT, nor on blood pressure, and thus was non differential. Therefore, any misclassification in either of these studies can be assumed to have a low risk of bias and thus may have led to a dilution of the effect. The almost 10-fold difference in number of participants might explain why we did find an association between blood pressure and apathy in the large AGES-Reykjavik Study (n=4,041) but not between hs-cTnT and apathy in the smaller Leiden 85-plus Study (n=455). Another disadvantage we experienced when using the GDS-3A in our studies, was the limited possibility to analyze it as a continuous scale, while this would render more efficient analyses and would be a better representation of the variation in clinical practice. Despite all these limitations, the availability of the GDS-3A in the Leiden 85-Plus Study and the AGES-Reykjavik Study provided us with the important opportunity to study apathy separately from depression and cognitive dysfunction.

## Cardiac biomarkers and neurocognitive functioning

In **chapter 3,** we have demonstrated that higher levels of hs-c-TnT are associated with worse cognitive function in a population of the oldest old, and that those with the highest levels of hs-cTnT have the steepest annual decline in cognitive function during four years of follow-up. This association was independent of important potential common causes (confounders), such as renal function and cardiovascular risk factors. Moreover, the association was also present when we restricted our analyses to those without a history of clinically overt cardiac disease. Importantly, the association between higher levels of hs-cTnT and worse cognitive function in this group of the oldest old, is similar to the direction of effect found in younger study populations[7].

Our study is among the few that investigated the association between hs-cTnT and cognitive function[8]. More evidence is available that N-terminal pro-Brain Natriuretic Peptide (NT pro-BNP), a widely used clinical marker for disease severity in heart failure, is also related to worse cognitive functioning[8]. Since there is no evidence that hs-cTnT itself has a biological action in brain tissue, it can be considered a risk marker for adverse health outcomes, even in the absence of clinically overt cardiac disease[9-11]. NT pro-BNP on the other hand, is proposed to have regulatory functions in the brain[12]. For both hs-cTnT and NT-proBNP, the added value for identifying those individuals at greatest risk for cognitive decline has yet to be determined[13, 14].

## Functional status and cerebral small vessel disease affect the relation between late-life blood pressure and neurocognitive functioning

While the harmful effects of midlife hypertension have been irrevocably shown[15,16], controversy remains regarding the association between late-life blood pressure and adverse brain health outcomes. Previous studies found that both a higher and a lower late-life blood pressure were related to stroke[17], functional decline[18], and cognitive dysfunction[19]. The literature also showed conflicting results for the association between late-life blood pressure and apathy. In contrast to a few other studies[20,21], we found a lower and not a higher late-life blood pressure to be associated with more symptoms of apathy. Further, in line with other both cross sectional[22,23] and longitudinal[24] studies among older persons, we showed an association between lower blood pressure and more depressive symptoms in the AGES-Reykjavik Study (**chapter 6**), whereas in the DANTE Study Leiden blood pressure appeared not to be related to depressive symptoms (**chapters 4** and **5**).
It has been suggested that differences in population characteristics underlie these different directions of associations found to date[25,26]. This hypothesis is supported by several studies regarding cognitive dysfunction that demonstrated that lower blood pressure was specifically or especially related to adverse brain outcomes in the oldest old versus younger-old adults[27,28], in those with midlife hypertension but not in those without[29], and in those with worse but not better physical function[17,28-30].

**Is a lower blood pressure always better?**

Our hypothesis was that specifically in those older persons with impaired cerebral autoregulation, cerebral blood flow (CBF) would be more dependent on systemic blood pressure and thus, lower blood pressure might lead to worse neurocognitive functioning. Indeed, in both the DANTE Study Leiden (**chapter 4** and **5**) and the AGES-Reykjavik Study (**chapter 6**) we found a consistent pattern of a cross sectional association between lower blood pressure and symptoms of apathy specifically in those with worse functional ability and more CSVD. These subgroups might represent those older persons with an impaired cerebral autoregulation and for these subgroups, the common adage 'the lower the better' might not hold for late-life blood pressure. However, given the cross-sectional design of our studies, causal mechanisms can only be hypothesized, not inferred.
For our study, we used baseline data from the DANTE Study Leiden and our findings should be regarded in light of the findings of the trial. For the DANTE Study Leiden trial, 356 participants were randomized into either discontinuation (intervention, n=180) or continuation (control, n=176) of antihypertensive treatment[31]. Blood pressure was measured at 8, 12, and 16 weeks and neurocognitive outcomes were

re-assessed at 16 weeks. Intervention allocation was blinded and the researchers who performed the outcome assessment were blinded for the intervention arms; participants and their treating physicians were not blinded. The trial showed that, while mean blood pressure indeed increased in the discontinuation arm, no effect was found on cognitive function, symptoms of depression, or symptoms of apathy. Additionally, when stratifying for functional ability and features of CSVD, no differences in effect were found either[31]. Potentially, a follow-up period of 16 weeks is too short to render an effect on neurocognitive functioning. However, in contrast to the hypoperfusion hypothesis, results from the DANTE Study Leiden MRI Sub Study showed that discontinuation of antihypertensive treatment did not alter cerebral blood flow, not even so after stratifying for functional ability and features of CSVD[32]. Moreover, no association between baseline blood pressure and baseline CBF was found[32]. It could be argued that cerebral autoregulation was intact in the DANTE Study Leiden population, and thus CBF did not depend on systemic blood pressure. Other studies also failed to show an association between lower blood pressure and CBF[33], or demonstrated an association between higher blood pressure and lower CBF[34]. Although it has been repeatedly shown that CBF is lower in patients with major neurocognitive disorder (dementia)[35, 36], it is still under debate whether this is a cause of dementia-related pathologies[37], or whether neurodegeneration in specific brain areas precedes a reduced cerebral blood flow[38]. As our cross-sectional data in the DANTE Study Leiden and the AGES-Reykjavik Study did not allow us to determine the temporal association between blood pressure and neurocognitive functioning, the directionality of the effect can only be hypothesized on. While in the longitudinal Leiden 85-Plus Study vascular disease was associated with incident apathy[6], a meta-analysis using individual patient data at the same time showed that apathy was related to incident myocardial infarction, stroke, and all cause mortality[4]. Specifically, symptoms of apathy such as less goal directed behavior and reduced interest in activities, could lead to unfavorable lifestyle changes and thus influence vascular risk.

For the association between blood pressure and cognitive dysfunction, it has also been proposed that neurodegenerative processes in the brain influence regulation of blood pressure[39]. The DANTE Study Leiden found no short-term effect of the elevation of blood pressure on neurocognitive functioning. A recent meta-analysis using individual patient data demonstrated that antihypertensive treatment in older persons >65 years was associated with a reduced risk of dementia after 5 years in clinical trials, but found no such an effect in cohort studies[40]. In the recently conducted SPRINT-MIND trial those older persons receiving intensive blood pressure lowering treatment (to ≤120 mmHg) had a lower risk of mild cognitive impairment (MCI), but not dementia[41]. While this result was also found in a sub analysis of those persons aged >75 years, the SPRINT-MIND trial included very few of the (frail) oldest old

and participants were relatively healthy. While these results suggest that changes in blood pressure precede the development of neurocognitive symptoms, it still has to be demonstrated whether specific subgroups of older persons might benefit from higher rather than lower blood pressure. The DANTON Study[42] strives to answer this question in a discontinuation trial design among nursing home patients.

**What is the role for cardiac function?**

One important factor that might be related to both a lower blood pressure[43] and worse neurocognitive functioning[44], is a reduced cardiac function. By design, the DANTE Study Leiden excluded those older persons with clinically overt heart failure because of safety reasons, and also excluded those with a recent major cardiovascular event[31], and we adjusted our analyses for cardiovascular risk factors and older cardiovascular events. In the AGES-Reykjavik Study, we adjusted for a diagnosis of heart failure and for other cardiovascular diseases and risk factors. However, a sub-clinically reduced cardiac function may still be a common cause of both lower blood pressure and worse neurocognitive function. Alternatively, the presence of worse cardiac function might modify the association between blood pressure and neurocognitive functioning, as a study among participants of the Leiden 85-Plus Study found that especially in those with a higher level of N Terminal pro-Brain Natriuretic Peptide, a marker for heart failure severity, lower blood pressure was associated with worse cognitive functioning[45].

## Methodological considerations

**Strengths**

Strengths of the methods used in this thesis include the use of multiple well-described study populations including older people along a wide range of age. These studies were rigorously designed, and measurement of determinants, outcomes and potential confounders was done in a valid and standardized way. For both the research questions on the validity of the GDS-3A and the associations between blood pressure and symptoms of apathy and depression, we used two separate patient populations, leading to a more robust interpretation of our findings. By performing the research on the validity of the GDS-3A as a measure for apathy, we were much aware of the potential pitfalls when we used the GDS-3A in our analyses on risk factors for apathy.

**Limitations**

The studies presented in this thesis come with methodological limitations inherent to the designs and our analytical approaches. While the DANTE Study

Leiden has a unique study population of older persons, the fact that people were selected to participate in a clinical trial limits the generalizability of the results. All participants used antihypertensive medication, while the prevalence of a history of cardiovascular disease was relatively low since older persons with a history of a severe cardio- and cerebrovascular event were excluded for safety reasons. For our work on the validity of the GDS-3A we were able to compare the results from the DANTE Study Leiden with the population of the PROMODE Study. While the PROMODE Study was also designed as a randomized clinical trial, the data on the GDS-3A and Apathy Scale were collected in the screening phase of this study for which fewer in- and exclusion criteria applied[46]. Further, our results on the association between lower blood pressure and apathy in the DANTE Study Leiden were in line with our findings in the AGES-Reykjavik Study, a large study population for which very few selection criteria existed. This provides confidence that results may be generalizable to a larger population of older persons.

Besides methodological challenges concerning the lack of a gold standard for measuring apathy as discussed before, also no standard definition of cerebral small vessel disease across different studies is available as of yet[47]. While white matter hyperintensities, lacunar infarcts, and cerebral microbleeds were available in both the DANTE Study Leiden and AGES-Reykjavik Study, perivascular spaces (Virchow-Robin spaces) were only measured in the latter and included in the sum score of CSVD[47]. We included global cortical atrophy in the total CSVD score in **chapter 6** to make the definition of CSVD comparable across papers from the AGES-Reykjavik Study[48]. In the DANTE Study Leiden in **chapter 5**, however, we separated this analysis from our main analyses because of the ongoing discussion whether global cortical brain atrophy should be part of the definition of CSVD or that it should be regarded as a marker that is more specific for neurodegeneration[49]. To increase comparability between the studies in this thesis we added global cortical atrophy to the total CSVD score in an additional analysis of the DANTE Study Leiden in **chapter 5**, which did not alter the results.

All of our conclusions come from observational studies, which hampers explicit causal inference and direct translation into clinical practice. Observational data is prone to bias from confounding, when common causes of both the exposure and outcome are present. In each of our studies, we attempted to adjust for confounding by analyzing the association of interest in different models comprising potential confounders. These potential confounders were selected on knowledge of their association with the determent and outcome based on previous studies rather than by a data driven method. However, not all potential confounders were measured in each study, leaving room for residual confounding in our study results.

While targeting an older study population is important to be able to generalize study results to real life patients, selecting older persons for participation in observational

studies carries a risk of survival bias. Specifically, the very characteristics that allowed a study population to survive into old age despite a risk factor (e.g. hypertension) for mortality, might also be the characteristics that protect their neurocognitive function. As of yet, there is still substantial controversy on how to quantify the magnitude of the bias in real life data and how to subsequently address these issues in data analyses.

## Clinical implications

We demonstrated that the GDS-3A only has a moderate discriminatory value for the presence or absence of apathy. Until future studies demonstrate whether the GDS-3A as a separate instrument has an added value in the screening process for apathy, we advise to use other instruments such as the Neuropsychiatric Inventory and the Apathy Scale as measures in clinical practice.

Because of methodological limitations intrinsic to the observational designs, our studies on cardiovascular and hemodynamic risk factors for neurocognitive function in older age cannot be directly applied in clinical practice. However, the notion that apathy, depression and cognitive dysfunction have different risk factor profiles can be translated into clinical practice, albeit indirectly. In patients presenting with reduced goal-directed behavior and lack of interest, physicians should be aware that in the absence of overt cognitive dysfunction and purely mood symptoms, an apathy syndrome may be present. If so, based on the findings in this thesis and others before us, awareness of a potential connection with vascular disease and risk factors should prompt physicians to assess vascular (risk) status. Vice versa, in patients undergoing both cardiovascular and neurocognitive evaluation, such as is increasingly implemented in so-called *heart-brain clinics*[50], it is important to measure symptoms of apathy and depression in each patient.



## Recommendations for future studies

**Measuring apathy in research settings**

For future studies, we stress the importance of the use of a specific instrument to measure apathy. Because in the DANTE Study Leiden and the PROMODE Study the GDS-3A was administered as part of the whole GDS-15, it is uncertain how the GDS-3A would perform if the three questions were to be administered separately to screen for apathy. Until evidence on measuring apathy becomes more conclusive, we recommend researchers to scrutinize the available instruments and to choose the instrument that best fits the purpose of the study in terms of feasibility and test

characteristics. The Neuropsychiatric Inventory (NPI)[51] has the benefit that it is informant-based, easy to administer, and that it provides both a presence/absence answer and a severity scale. However, its validity has mostly been studied in clinical populations with dementia[52] and it might be less useful to detect apathy in populations with better cognitive function. The Starkstein Apathy Scale is relatively brief and shows favorable characteristics of reliability and validity, but has been tested in a limited number of populations[52]. It is based on the Apathy Evaluation Scale, a more elaborate scale which may take longer to administer but which is validated in different study populations[52]. When using the GDS-3A, we advise to use it specifically in larger study populations with a higher estimated prevalence such as in older persons, and we stress the importance to take caution in interpreting negative findings as evidence for absence of and association.

**Novel methodological approaches**

One of the premises for the DANTE Study Leiden was that clinical trials in the past tended to exclude older persons and thus generalizability of findings of RCTs to older populations was an issue in clinical practice. Moreover, the concept of 'precision medicine', addressing the clinician's question of 'will this intervention work for this particular patient', has led to the investigation of heterogeneous treatment effects in randomized controlled trials (RCT)[53]. While RCTs generally are considered the golden standard in providing evidence concerning treatment effects, observational studies will continue to provide important hypotheses on potential risk factors that RCTs can be designed from, and in providing evidence on risk factors or interventions that cannot be randomized because of practical or ethical reasons. An intriguing new research direction is the investigation of multiple heterogeneous exposure associations in observational studies. A recent study[25] presented a sophisticated data driven model to investigate combinations of potential effect modifying characteristics for the association between systolic blood pressure and mortality. While these strategies generally require large study populations and do not provide solutions for all assumptions that need to be met for causal inference, they might provide more insight into disease mechanisms and could help target patient populations that might benefit from or be harmed by blood pressure lowering strategies.

To strengthen the evidence on risk factors for dementia in observational studies, important researchers in the field started the MEthods in LOngitudinal research on DEMentia (MELODEM) initiative[54]. In line with the CONsolidated Standards of Reporting Trials (CONSORT)[55] and Strengthening the Reporting of Observational studies in Epidemiology (STROBE)[56] guidelines, the MELODEM initiative strives to unify the reporting of potential sources of bias in observational longitudinal studies on cognitive outcomes. Importantly, the MELODEM initiative focuses on

methodological challenges for longitudinal studies on cognitive dysfunction, and not on other neurocognitive outcomes such as apathy and depression. As we have shown in this thesis, issues concerning measurement are irrevocably of equal importance when investigating depressive symptoms and particularly apathy as an outcome of interest. However, while cognitive decline typically is a slowly progressive process, the longitudinal course of apathy in later life is much less investigated, and depressive symptoms tend to fluctuate much more than cognitive dysfunction. It therefore remains important to address potential sources of bias for each research question individually, based on the determinant and outcome of interest, and the study population at hand[57].

**The Heart-Brain Study: unraveling the role of cardiac function and hemodynamic balance in neurocognitive functioning**

Our studies have contributed to disentangling the intriguing relation between structural cardio- and cerebrovascular damage, hemodynamic changes, and neurocognitive outcomes, and gave rise to a number of new hypotheses. The Heart-Brain Study(HBS)[58], as part of the larger Heart-Brain Connection Consortium[59], was designed to investigate the complete heart-brain-axis in patients with disturbances of (parts of) the axis, including patients with heart failure, carotid occlusive disease, and vascular cognitive impairment. All patients underwent an extensive clinical protocol, cardiac and cerebral magnetic resonance imaging (MRI), and an elaborate neurocognitive testing battery, including symptoms of depression (measured with the GDS-15) and apathy (measured with the Apathy Scale). These data provide the opportunity to investigate the relation between cardiac function and blood pressure on the one hand, and neurocognitive function on the other hand. Further, the role of CBF in these associations can be tested, as well as the influence of cardiac function on the association between blood pressure and neurocognitive functioning.

After two years, all participants of the Heart-Brain Study underwent a follow-up measurement. Thus, the temporality of a potential association between vascular and hemodynamic factors and neurocognitive function can be further studied. This is especially important for apathy, since longitudinal data on the determinants of progression of, or recovery from, apathy are scarce. Since apathy, depression, and cognitive dysfunction can be studied separately in the Heart-Brain Study, results from this study will contribute to a further understanding of the involvement of hemodynamic disturbances in neurocognitive functioning in older persons.

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