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

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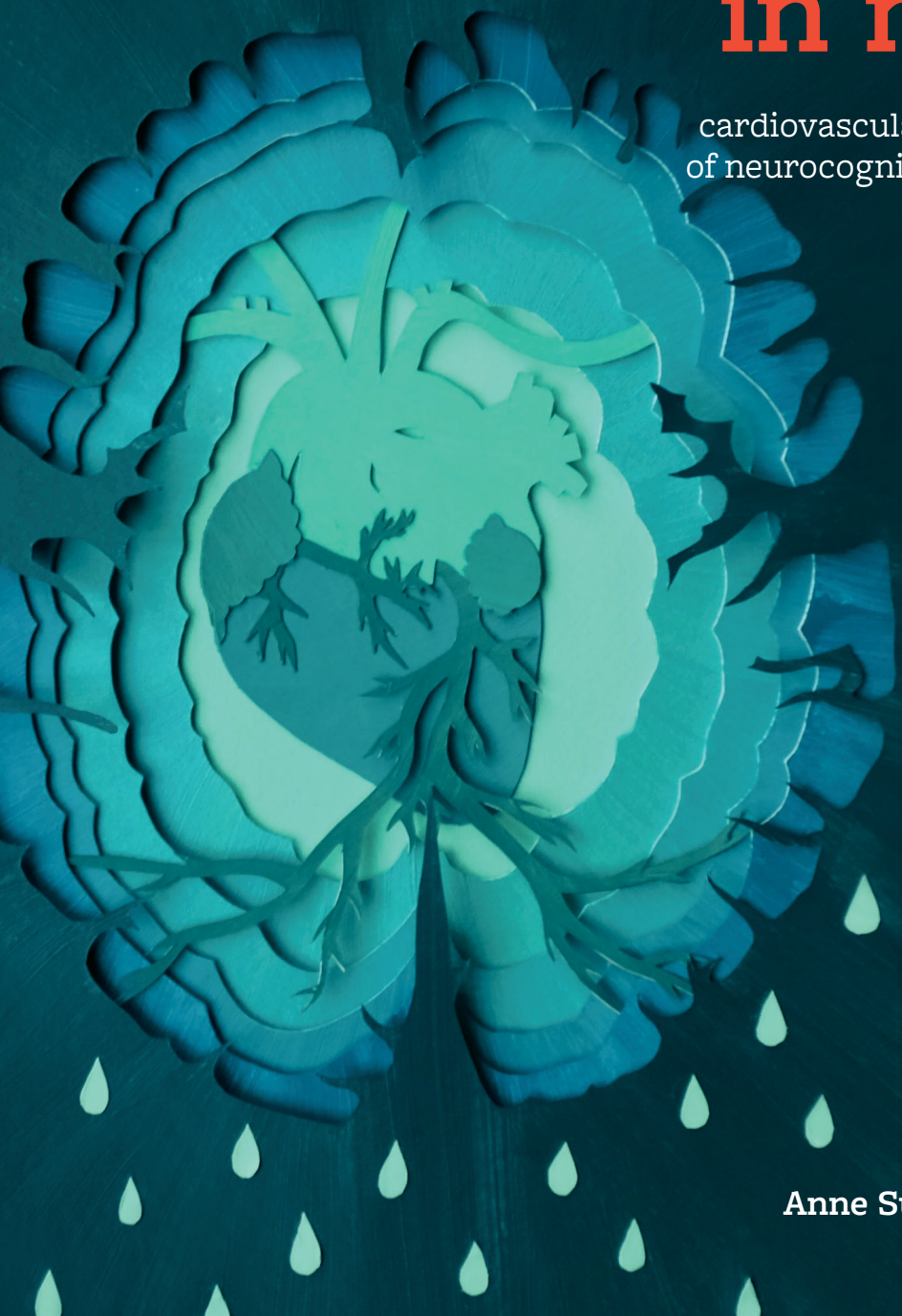

Anne Suzanne Bertens

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Keeping the heart in mind

Cardiovascular determinants of neurocognitive functioning in old age

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Voor mijn vader

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Chapter 1

General introduction

Neurocognitive functioning in older people

The clinical picture of patients with dementia is particularly associated with a decline in memory function. However, memory is merely one of the cognitive domains that can deteriorate to interfere significantly with daily functioning, the latter being imperative for the diagnosis of dementia[1]. Patients can also lose the ability to organize their finances (executive dysfunction), have trouble finding the right words to express themselves (language problems), or exhibit disturbed behavior that could severely damage their relationships with loved ones (problems with social cognition). By recognizing the full clinical picture of cognitive decline or dementia, scientific research can target those problems that are of consequence for real-life patients.

To describe this broader clinical spectrum of cognitive decline, the Diagnostic and Statistical Manual (DSM)-5 of Mental Disorders, which is being used as a uniform classification system for clinical practice and research in psychiatry, introduced the term 'major neurocognitive disorder' (NCD) to replace the term dementia[1]. Apart from the domain memory and learning, the cognitive domains comprise complex attention, executive dysfunction, language, perceptual motor function, and social cognition. Besides cognitive decline, patients can present with what the DSM-5 classifies as auxiliary 'behavioral disturbances' such as mood symptoms, apathy, irritability, sleep and eating disturbances, and psychotic symptoms[1]. These behavioral disturbances, in the literature often referred to as neuropsychiatric symptoms, are highly prevalent [2-4], can be particularly burdensome[5, 6], and can also occur outside the scope of cognitive dysfunction[7]. However, as research often focusses primarily on cognitive decline and dysfunction in the different cognitive domains, much less is known of specific risk factors and potential targets for treatment for these disabling neuropsychiatric symptoms. To capture the array of symptoms older patients can present with, in this thesis, the term 'neurocognitive functioning' will be used as an umbrella term for both cognitive (dys)functioning and neuropsychiatric symptoms. Phenomena of apathy and depression are among the most prevalent symptoms[2-4], and, together with cognitive dysfunction[8], these are most frequently associated with cardiovascular factors[9, 10]. Therefore, this thesis will focus on cognitive dysfunction as well as symptoms of apathy and depression as primary outcomes of interest.

Apathy, depression, and cognition in old age

Apathy as a clinical syndrome, distinct from depression and cognitive dysfunction

Apathy, defined as reduced motivation and goal directed behavior, diminished emotions, and less engagement in social interaction[11], can be part of depression[12] but is increasingly regarded as a symptom in its own right[13]. The two key symptoms of depression are a depressed mood and loss of interest. Clinicians noted that a marked proportion of older persons presented especially with this loss of interest and lack of motivation, but with no altered mood and with few of the other typical depressive symptoms such as hopelessness, weight and sleep changes, and suicidal thoughts[14]. As results from antidepressant treatment were also disappointing in these patients, it was proposed that these patients did not suffer from depression but rather from apathy as a distinct clinical syndrome[14]. When regarded as such, apathy is a frequent and disabling symptom in patients with major NCD (= dementia)[4] , but also occurs in those with minor NCD (=mild cognitive impairment)[3] and even in community dwelling older persons without cognitive dysfunction[7, 15, 16]. This implies a symptom overlap not only with depression, but also with cognitive dysfunction. Figure 1.1 not only shows the overlapping, but also the distinct symptoms of apathy, depression, and cognitive dysfunction, which is of relevance to both clinical practice and research.

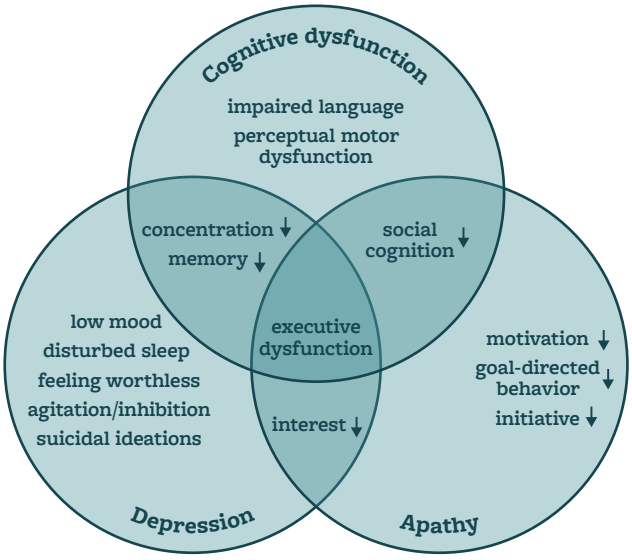

Figure 1.1 Overlap between cognitive dysfunction, depression, and apathy

It is important to correctly diagnose an older patient presenting with loss of interest, for this determines which treatment strategy a clinician proposes (e.g., psychotherapy and/or pharmacological antidepressant treatment in case of a clinical depression) or what psychoeducation she gives on the prognosis of disease progression (e.g., in the case of a diagnosis of major NCD). To enable clinicians to provide patients and their families with the correct information, researchers have to distinguish apathy from depression and cognitive dysfunction when investigating specific modifiable risk factors, studying treatment strategies, and determining symptom courses over time. It is especially important to separately address apathy, since far less is known on its specific risk factors in old age while it is associated with a high care giver burden[17], poor functional ability[18], and even mortality[19].

Measurement of symptoms of apathy in research settings

To investigate modifiable risk factors and potential treatment strategies, it is pivotal that apathy is adequately assessed in research settings. While symptoms of depression are frequently measured in large observational studies[20-22], a specific instrument for apathy such as the Apathy Scale[23] is scarcely being administered. Because apathy is increasingly prioritized in recent studies among older people, researchers have explored proxy instruments. The Geriatric Depression Scale (GDS)-15 is often used to screen for late-life depressive symptoms in research as well as in clinical practice, and has a good validity and inter rater reliability[24]. Factor analyses[25, 26] and expert panels[26] have identified three questions of the GDS-15 that assess symptoms of apathy, namely (1) have you dropped many of your activities and interests?; (2) do you prefer to stay at home, rather than go out and doing new things?; and (3) do you feel full of energy?. This subset, the GDS-3A, was first used by Van der Mast *et al.* to investigate risk factors for apathy and has been increasingly used since[16, 22, 26]. However, research into the scale properties of the GDS-3A is limited[26]. It is, therefore, important to know the epidemiological test characteristics such as sensitivity and specificity to determine the validity of the use of the GDS-3A to study potentially modifiable risk factors for apathy.

Cardiovascular determinants and neurocognitive functioning

Cognitive dysfunction, symptoms of apathy, and depressive symptoms in late life may have distinct risk factor patterns, and cardiovascular determinants may play an important role in all three. While the association between cardiovascular disease and cognitive dysfunction has been well established and consolidated in the clinically widely used diagnosis of *vascular cognitive impairment*[27], the link with symptoms of depression and apathy to date is less straightforward[28-31].

Vascular depression?

In the late 1990s, the concept of a vascular depression was postulated[32]. Clinicians observed a phenotype of late-life depression in which lack of initiative and motivation, as well as executive dysfunction, were more prominently present than purely 'mood' symptoms such as feelings of worthlessness and suicidal ideations. In the era of the rising use of neuro-imaging techniques, researchers observed that this particular phenotype was more often accompanied by vascular damage on computer tomography (CT) images of the brain, and the term vascular depression was coined[32]. At the same time, it was also observed that these depressive symptoms were more often associated with the presence of cardiovascular risk factors[32]. However, the temporality of these associations has been debated, as studies have shown both an increased risk of future depression in those with a higher burden of cardiovascular risk factors[30], as an increased risk of future myocardial infarction in patients with a depression[31]. Moreover, since depression measures often include items that represent apathy, it could be hypothesized that these studies have assessed associations with apathy rather than depression.

Vascular apathy?

In recent years, it has been suggested that the syndrome of vascular depression might actually be more accurately described as vascular apathy[10, 22, 26]. Exactly those symptoms that were most prominently seen in 'vascular depression', namely lack of interest and motivation in the absence of a depressed mood, are considered part of the apathy syndrome[11]. Further, studies have shown that cardiovascular factors and diseases were more often linked to symptoms of apathy than of a depressed mood[25, 26] and a recent review described how cerebral small vessel disease (CSVD) is increasingly found to be associated with apathy[10]. However, also for apathy a bidirectional association with cardiovascular disease has been described[22]. Thus, the exact mechanisms behind these associations have yet to be elucidated.

Taylor *et al.*[9] proposed a model for the pathogenesis of vascular depression (Figure 1.2) and described a pathway from cardiovascular determinants to depression, both through direct structural cerebrovascular damage and through impaired cerebral perfusion. This model, while not claimed to be conclusive, might also apply to cognitive impairment and apathy. Alternatively, specific risk factors might be differentially associated with these distinct outcomes. However, few studies have incorporated cognitive impairment, depressive symptoms, and apathy in one study design, hampering direct conclusions on specific risk factor patterns.

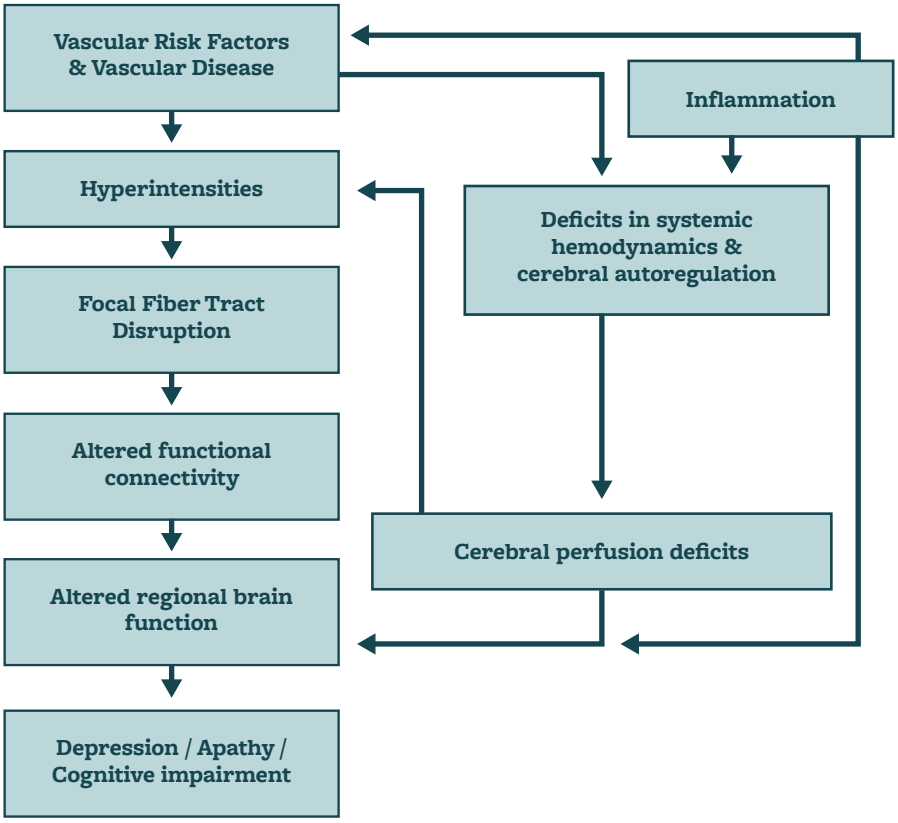

Figure 1.2 Proposed mechanisms for cardiovascular determinants of neurocognitive functioning

With permission adapted from Taylor et al. Molecular Psychiatry (2013) 18, 963–974.

There is increasing evidence that cardiac disease in particular might play an important role in adverse brain outcomes[33-35]. To establish the presence and degree of cardiac disease, serum cardiac markers such as natriuretic peptides and cardiac troponins are frequently measured in clinical practice. While the clinical role of high sensitivity cardiac troponin T (hs-c-TnT) lies mainly in the diagnostic work up for myocardial infarction[36], there is increasing evidence that also in the absence of acute myocardial infarction, higher levels of hs-cTnT are related to a higher cardiovascular morbidity and mortality[37]. Higher levels of hs-cTnT have also been related to adverse brain outcomes including cognitive decline[38, 39], but these studies have included mainly middle-aged or younger-old persons. Moreover, these studies have not looked into a possible association between hs-cTnT and symptoms of depression and apathy, and have not specifically addressed the role of overt cardiac disease in these associations.

Blood pressure and neurocognitive functioning

While vascular risk factors could lead to worse neurocognitive functioning through direct cerebrovascular damage, deficits in systemic hemodynamics and cerebral perfusion might also play an important role, as shown in Figure 1.2[9]. In this respect, it is important to consider the role of systemic blood pressure since it can be readily measured and rather easily be intervened upon, making it a potentially modifiable risk factor. The detrimental effect of midlife hypertension (commonly defined as a systolic blood pressure of <140 mmHg and/or a diastolic blood pressure of >90 mmHg) has been well-established. Not only does hypertension have a role in the risk of classical cardiovascular diseases such as myocardial infarction[40], but it has also been widely acknowledged that hypertension in midlife is associated with cognitive decline and dementia in older age[8, 41, 42]. However, the association between late-life blood pressure and adverse outcomes is less straight forward. Several observational studies found that lower rather than higher late-life (≥75 years) blood pressure was related to adverse brain outcomes including worse cognitive function[43-45]. In contrast, the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE)-Study Leiden, a randomized clinical trial among older persons (≥75 years) with mild cognitive deficits, did not find a favorable effect of elevating blood pressure on neurocognitive functioning[46]. Heterogeneity in population characteristics might underlie these contrasting findings[47]. Indeed, both cross-sectional[48] and longitudinal studies[49, 50] have shown that lower blood pressure was particularly related to worse cognitive function in those older persons with worse functional ability. Thus far, the few studies among relatively younger older persons that have investigated apathy, found however that higher and not lower blood pressure was a risk factor[25, 51], whereas both a higher[52] and a lower blood pressure[53, 54] have been associated with depressive symptoms in later life. It has yet to be investigated whether population characteristics such as functional ability also play a role in the relation between late-life blood pressure and symptoms of apathy and depression.

A role for cerebral small vessel disease in neurocognitive functioning?

One of the proposed mechanisms through which lower late-life blood pressure might lead to worse neurocognitive functioning in older persons with worse functional ability, is through reduced cerebral blood flow in brain areas involved in regulating cognitive function, mood, and motivation[55]. While the healthy brain is able to keep cerebral blood flow constant during changes in systemic blood pressure[56], this mechanism of cerebral autoregulation might be impaired by vascular damage[57, 58], which hypothetically may lead to reduced cerebral blood flow[59]. Although the exact mechanism has yet to be elucidated, it has therefore been hypothesized that lower

systemic blood pressure might impair neurocognitive functioning specifically in individuals with more vascular brain damage[55]. This vascular brain damage may clinically be reflected by worse functional ability[60, 61], which could explain why particularly in these older persons an association between lower blood pressure and worse cognitive function has been repeatedly found[48-50].

In studies with available magnetic resonance imaging (MRI), (subclinical) damage to the arterioles and smaller vessels of the brain can be measured as features of cerebral small vessel disease (CSVD). These features comprise white matter hyperintensities, lacunar infarcts, cerebral microbleeds, and enlarged perivascular spaces, also known as Virchow-Robin spaces[62]. With technical and clinical aspects, e.g. MRI field strength and radiological definitions of CSVD features, differing between studies and hospitals[62], as of yet no widely practiced definition of clinically relevant CSVD is in use. Further, it is still under debate whether brain atrophy is a distinct feature of CSVD or whether it is a consequence of it[62].

Regarding individual markers, white matter hyperintensities have been most widely studied and associated with worse neurocognitive functioning, while increasing evidence suggests that also microbleeds and lacunar infarcts may play a role[63,64]. While it can easily be reasoned why specific lesion locations would relate to specific symptoms based on knowledge of brain structure and function, it appears that not only individual features but also the total burden of features of CSVD is of importance, as a higher total CSVD burden has been related to worse cognitive and daily functioning[61, 65] and to more depressive symptoms[66] and symptoms of apathy[10]. As of yet, it has not been studied whether vascular brain pathologies as reflected by CSVD, have a role in the relation between blood pressure and neurocognitive functioning.

General aim and outline of this thesis

The aim of this thesis is to investigate cardiovascular determinants of neurocognitive functioning in old age, in particular cognitive dysfunction, depressive symptoms, and apathy.

First, we seek to investigate whether the GDS-3A, a sub set of the frequently used GDS-15, can be used to measure symptoms of apathy in research settings. In **chapter 2,** we therefore investigate the scale properties of the GDS-3A compared to the Apathy Scale in both the DANTE Study Leiden and the PROMODE Study.

Next, we aim to explore the relation between cardiac biomarkers and neurocognitive functioning. Therefore, in **chapter 3**, we study the longitudinal association between high sensitivity troponin T and neurocognitive functioning in the oldest old, using data from the Leiden 85-Plus Study.

The subsequent chapters focus on the role of markers of (vascular) brain damage in the association between blood pressure and neurocognitive functioning. In **chapter 4,** we investigate in the DANTE Study Leiden whether the association between blood pressure and symptoms of apathy and depression is different for older persons with varying levels of functional ability. In **chapter 5,** we study the role of cerebral small vessel disease in the association between blood pressure and symptoms of apathy and depression in the DANTE Study Leiden. These analyses were extended to cognitive function and the AGES-Reykjavik population in **chapter 6.** We hypothesize that lower blood pressure is related to worse neurocognitive functioning in sub groups of older persons with more (vascular) brain damage.
To conclude, **chapter 7** provides a general discussion of the main findings of this thesis and perspectives for future research. In **chapter 8**, the main findings are summarized.

Description of studies in this thesis

To test our hypotheses and answer our research questions we use data from four different population-based study cohorts that included older people.

The DANTE Study Leiden

The Discontinuation of ANtihypertensive Treatment in the Elderly (DANTE) Study Leiden included community dwelling older persons (aged 75 and older from the Leiden area, the Netherlands) with mild cognitive deficits (MMSE score 21-27, no diagnosis of dementia), using antihypertensive medication, and without a history of major cardiovascular disease[46]. The main aim of the DANTE Study Leiden was to investigate the effect of discontinuation of antihypertensive treatment on cognitive disfunction in a randomized controlled trial design. A baseline measurement including blood pressure and neurocognitive functioning (cognitive tests, GDS-15, Apathy Scale) was performed in 430 participants, and 210 of those also underwent MRI at baseline.

The PROMODE Study

The PROactive Management Of Depression in the Elderly (PROMODE) Study investigated the effect of a stepped-care intervention program among older persons (aged 75 years and older from the western part of the Netherlands) with depressive symptoms, but without a current treatment for depression or a diagnosis of dementia[67] in the western part of the Netherlands. A baseline measurement including the GDS-15 and Apathy Scale was performed in 1118 participants.

The Leiden 85-Plus Study

The Leiden 85-Plus Study invited all inhabitants of the city of Leiden (the Netherlands) who reached the age of 85 between 1997 and 1999, without applying eligibility criteria[68]. Hs-cTnT was determined at the age of 86, which we considered the baseline for our study. The 455 participants with available data on neurocognitive functioning (cognitive tests, GDS-15), hs-cTnT, and covariates at the age of 86 were selected for our analyses.

The AGES-Reykjavik Study

The Age Gene/Environment Susceptibility (AGES)-Reykjavik Study is a population based cohort study among community dwelling older persons (aged 75 years and older from Reykjavik, Iceland)[20]. A baseline assessment including blood pressure, neurocognitive functioning (cognitive tests, GDS-15), and MRI was performed in 4,014 participants, excluding those with a diagnosis of dementia.

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Chapter 2

Validity of the three apathy items of the Geriatric Depression Scale (GDS-3A) in measuring apathy in older persons

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Abstract

Objective: The Geriatric Depression Scale (GDS)-3A, a three-item subset of the GDS-15, is increasingly used as a measure for apathy in research settings to assess factors associating with this neuropsychiatric syndrome. We aimed to assess how accurately the GDS-3A discriminates between presence and absence of apathy in two populations of community-dwelling older persons, using the Apathy Scale as reference standard.

Methods: Baseline data were used from 427 participants of the Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden and 1118 participants of the PROactive Management Of Depression in the Elderly (PROMODE) Study, all ≥75 years and with available GDS-3A and Apathy Scale measurements. A cut-off score of ≥14 was used for presence of apathy according to the Apathy Scale. Areas under the receiver operating characteristic curve (AUC) were calculated. Based on the likelihood ratios for GDS-3A scores, a cut-off of ≥2 was used for presence of apathy according to the GDS-3A to calculate test characteristics.

Results: The AUC was 0.68 (95% confidence interval 0.62-0.73) in the DANTE Study and 0.72 (0.67-0.77) in the PROMODE Study. In the DANTE Study sensitivity was 29.3% (21.4-38.1) and specificity was 88.5% (84.4-91.8), whereas in the PROMODE Study sensitivity was 32.8% (24.5-41.1) and specificity 92.6% (90.9-94.2). Stratification on population characteristics did not yield more favourable test characteristics.

Conclusion: The GDS-3A has low sensitivity and high specificity as a measure of apathy in two populations of older persons. Using the GDS-3A in research might yield estimates biased towards the null in case of non-differential misclassification.

Introduction

Apathy is an important yet often overlooked neuropsychiatric behavioural syndrome that is common in older persons[1, 2]. Apathy is characterized by diminished motivation and initiative, reduced goal-directed behaviour, loss of interest and emotional indifference[3, 4]. Its presence in older persons is associated with worse cognitive functioning[5, 6], reduced therapeutic response[1], lower quality of life[7, 8], and high caregiver distress[9]. While symptoms of apathy can occur as part of depression, apathy is increasingly being recognised as a syndrome in its own right, also in the absence of a depressed mood[3, 10, 11]. No valid, easily applicable screening tool for apathy is available for use in general clinical practice[12, 13]. Because of its association with adverse health outcomes, apathy is increasingly prioritised on research agendas, with subsequent expanding knowledge on its specific prognostic[14, 15] and possibly causal factors[16-18].

Data from large observational studies could be particularly useful in identifying potentially modifiable risk factors for apathy at old age. However, only few studies have used specific instruments to prospectively collect data on symptoms of apathy, whereas symptoms of depression are often measured[15, 19]. To screen for symptoms of depression at old age, the Geriatric Depression Scale (GDS)-15 is frequently used in clinical practice as well as in research, showing a good reliability and validity[20]. In factor analyses, a subset of three GDS-15 items has repeatedly been identified as a cluster of symptoms that assesses apathy[21-23]. This GDS-3-apathy subscale (GDS-3A) comprises the items: (1) Have you dropped many of your activities and interest?; (2) Do you prefer to stay at home, rather than going out and doing new things?; and (3) Do you feel full of energy? The GDS-3A subscale is increasingly being used in research to identify participants with apathy in studying associating factors[14-16]. However, only limited evidence exists for the discriminatory value of the GDS-3A for the presence or absence of clinically relevant apathy. Van der Mast *et al*. compared the GDS-3A with the Apathy Scale in a sample of community-dwelling 90-year-olds, rendering a sensitivity of 68.6%, a specificity of 84.9%, a positive predictive value of 77.8%, and a negative predictive value of 77.8%[14]. To the best of our knowledge, this is the only study providing epidemiological test characteristics for the GDS-3A and therefore it is yet undetermined whether these discriminatory qualities of the GDS-3A also hold for other populations of older persons.

In the Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden and the Proactive Management of Depression in the Elderly (PROMODE) Study both the GDS-3A and the Apathy Scale were assessed as part of a neuropsychological evaluation, providing the unique opportunity to compare these questionnaires in two large cohorts of older persons. Therefore, the aim of conducting the current study was to assess how accurately the GDS-3A discriminates

between presence and absence of apathy in two populations of community-dwelling older persons, compared to the Apathy Scale.

Methods

Study populations

We used baseline data of two Dutch randomised controlled trials, the DANTE Study and the PROMODE Study.

Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden

The primary aim of the DANTE trial was to assess whether discontinuation of antihypertensive treatment in older persons with mild cognitive deficits improves cognitive, psychological and general daily functioning[24] . Participants aged ≥75 years, using antihypertensive medication, with a current systolic blood pressure ≤160 mmHg, without serious cardiovascular disease, and without a diagnosis of dementia were recruited from primary care practices between May 2011 and July 2013. Of the 5537 selected older persons, 2002 consented to participate in a Mini Mental State Examination screening. A total of 1301 persons did not meet the MMSE selection criterion (MMSE score of 21-27), 67 did not meet other selection criteria, 204 declined to participate, and 3 had missing data on the Apathy Scale and/or the GDS-15, leaving 427 participants for further analyses.

PROactive Management Of Depression in the Elderly (PROMODE) Study

The primary aim of the PROMODE trial was to investigate the (cost-) effectiveness of a stepped-care intervention programme among older persons with depressive symptoms[25]. A total of 2759 participants aged 75 years and above were recruited from primary care practices between April 2007 and July 2008. A total of 366 persons were excluded because of a MMSE score of less than 19 points, a limited life expectancy, recent loss of partner, a diagnosis of dementia or a current treatment for depression. Of the remaining 2393 persons invited to participate, 1054 were non-responders, 101 did not meet selection criteria and 120 persons had inadequate assessment or missing data of the Apathy Scale, leaving 1118 participants for analyses[8].

The medical ethics committee of the Leiden University Medical Center approved both the DANTE and PROMODE Study, and informed consent was obtained from all participants. In the DANTE Study all participants had mild cognitive deficits and therefore gave informed consent after written and verbal description of the study was given in the presence of a close relative serving as a proxy decision maker[26].

Measurements

Geriatric Depression Scale (GDS)

In both studies, the GDS-15[27] was administered at baseline by trained research personnel to assess presence of depressive symptoms within the last few weeks. The GDS-15 is a short version of the GDS-30[27], and shows a good reliability and validity[20]. The scale consists of 15 items that can be scored as present or absent (range 0-15 point, with higher scores indicating more symptoms of depression). A score of five or higher is indicative of clinically relevant depressive symptoms[20]. The apathy subscale (GDS-3A) of the GDS-15 consists of the following 3 items (score range 0-3 points): (1)Have you dropped many of your activities and interest?; (2)Do you prefer to stay at home, rather than going out and doing new things?; and (3)Do you feel full of energy?

Apathy Scale

In both studies trained research personnel assessed the Apathy Scale to record presence of symptoms of apathy. The Apathy Scale, a semi-structured interview combining input from participants, proxy and clinical impression, is an abbreviated version of the Apathy Evaluation Scale[3], and has a good one-week test-retest reliability, inter-rater reliability and internal validity[28]. The Apathy Scale consists of 14 items that are scored on a four-point Likert scale (range 0-42 points, with higher scores indicating more symptoms of apathy). A score of at least 14 points is considered to be indicative for the presence of clinically relevant apathy[28]. The research personnel was not blinded for the GDS-15 scores.

Additional measurements

In both studies socio-demographic characteristics were assessed at baseline using standardized interviews. Level of education was dichotomized at primary education (six years of schooling) and use of alcohol was dichotomized at 14 consumptions per week. Global cognitive functioning was assessed with the MMSE (score range 0-30 points, with higher scores indicating better cognitive function)[29]. In the DANTE Study, presence of cardiovascular disease was obtained from the general practitioners using structured questionnaires, and defined as myocardial infarction or coronary reperfusion procedure longer than three years ago, and/or peripheral arterial disease, as persons with serious or recent cardiovascular disease (such as a history of stroke, transient ischemic attack or heart failure and/or a myocardial infarction/coronary reperfusion procedure within the last three years) were excluded from participation. No information regarding presence of cardiovascular disease was available in the PROMODE Study.

Statistical analyses

Characteristics of the study populations are presented as mean (standard deviation (SD)), number (%) or median (interquartile range (IQR)) when appropriate. In a receiver operating characteristic (ROC) curve the true positive rate (sensitivity) was plotted against the false positive rate (100-specificity) for different cut-off points of the GDS-3A, and the area under the curve was calculated. For each score on the GDS-3A, likelihood ratios were calculated: the proportion of participants with a specific test score in the presence of apathy was divided by the proportion of participants without apathy with that same test score. A two by two contingency table was created to determine the discriminatory accuracy of the GDS-3A using a cut-off of two or more points in assessing presence of apathy (according to ≥14 on the Apathy Scale). Sensitivity and specificity were calculated, as well as likelihood ratios for a positive (LR+) and negative (LR-) test using the following formulas: LR+ = sensitivity/(1-specificity) and LR- = (1-sensitivity)/specificity).

Spearman's correlation coefficients were computed for the GDS-3A and the Apathy Scale. To assess the influence of each item on the correlation of the GDS-3A with the Apathy Scale, these analyses were repeated after omitting either the first, second or third item of the GDS-3A. Furthermore, to assess whether discriminatory accuracy of the GDS-3A depended on population characteristics, we performed analyses in strata of age (of 5 years from 75 years onwards), gender, cognitive function (dichotomised at the median MMSE score), level of education (dichotomised at 6 years), and presence of cardiovascular disease (yes or no; only in the DANTE Study). Data were analysed using SPSS, version 22.0 and, Stata, version 12.0.

Results

In Table 2.1 the characteristics are shown of the 427 participants of the DANTE Study (mean age 81.3 (SD 4.6)) and the 1118 participants of the PROMODE Study (mean age 81.8 (SD 4.9)), with mean Apathy Scale scores of 11.3 (SD 4.7) and 7.5 (SD 4.6), respectively. Presence of apathy according to a score of ≥14 points on the Apathy Scale was 28.8% in the DANTE Study and 10.9% in the PROMODE Study.

Figure 2.1 presents the ROC curves, with areas under the ROC curves of 0.68 (95% confidence interval 0.62–0.73) in the DANTE Study and 0.72 (0.67–0.77) in the PROMODE Study.

In Table 2.2 the likelihood ratios for the individual GDS-3A scores are shown. In the DANTE Study, the likelihood ratio was 1.96 (1.18–3.25) for a score of two and 5.36 (2.08–13.8) for a score of three on the GDS-3A, while this was 4.32 (3.02–6.18) and 5.44 (1.56–19.0) respectively in the PROMODE Study.

Table 2.1 Characteristics of the DANTE Study and the PROMODE Study

	DANTE	PROMODE
Number of participants	427	1118
Age, years (mean, SD)	81.3 (4.6)	81.8 (4.9)
Female gender (n, %)	257 (60.2%)	684 (61.1)
Presence of CVD (n, %)[a]	48 (11.2%)	-[b]
MMSE score (median, IQR)	26 (25 - 27)	28 (27 - 29)
Lower level of education (n, %)[c]	142 (33.3%)	333 (29.8%)
Apathy Scale (mean, SD)	11.3 (4.7)	7.5 (4.6)
Apathy according to Apathy Scale (n, %)[d]	123 (28.8%)	122 (10.9%)
Apathy Scale score in those with apathy (mean, SD)	17.2 (3.3)	16.6 (2.8)
Scores on the GDS-3A (n, %)		
0	225 (52.8%)	718 (64.2%)
1	131 (30.7%)	286 (25.6%)
2	52 (12.2%)	104 (9.3%)
3	19 (4.4%)	10 (0.89%)
Depressive symptoms present (n, %)[e]	45 (10.5%)	64 (5.7%)

SD, standard deviation; CVD, cardiovascular disease; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale

a: Cardiovascular diseases comprise myocardial infarction or coronary intervention > 3 years ago, or presence of peripheral artery disease

b: No data on cardiovascular morbidity available in the PROMODE Study

c: Level of education is dichotomized at 6 years

d: Apathy according to the Apathy Scale: score of ≥14

e: Depressive symptoms present according to the GDS-15: score of ≥5

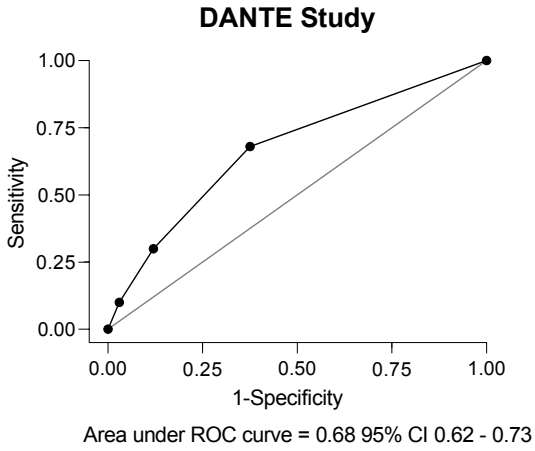
Table 2.2 Performance of the GDS-3A in the DANTE Study and the PROMODE Study

		DANTE Study (n=427)		
GDS-3A score	N	Apathy present[a]	Apathy absent	Likelihood ratio for GDS-3A score
3	19	13	6	5.36 (2.08 - 13.8)
2	52	23	29	1.96 (1.18 - 3.25)
1	131	50	81	1.53 (1.15 - 2.03)
0	225	37	188	0.49 (0.37 - 0.65)
Total	427	123	304	
		PROMODE Study (n=1118)		
GDS-3A score	N	Apathy present[a]	Apathy absent	Likelihood ratio for GDS-3A score
3	10	4	6	5.44 (1.56 - 19.0)
2	104	36	68	4.32 (3.02 - 6.18)
1	286	46	240	1.56 (1.21 - 2.02)
0	718	36	682	0.43 (0.33 - 0.57)
Total	1118	122	996	

Data are presented as numbers, or as likelihood ratios with 95% confidence intervals.

GDS, Geriatric Depression Scale

a: Apathy present: Apathy Scale score ≥14



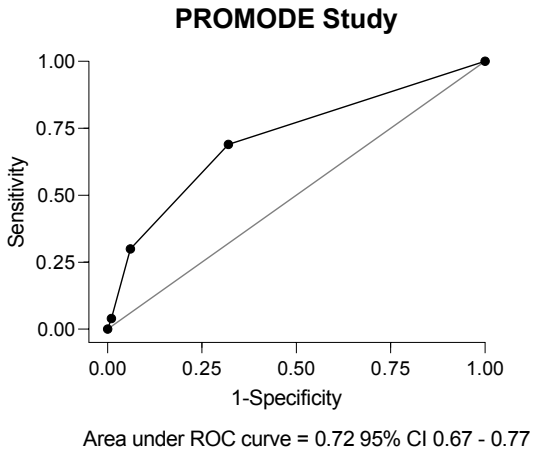


Figure 2.1 Receiver Operating Characteristic (ROC) curve for GDS-3A compared to the Apathy Scale in the DANTE Study and PROMODE Study

Since the percentage of participants scoring three points on the GDS-3A was low in both studies (n=19 for the DANTE Study and n=10 for the PROMODE Study), a cut-off score of ≥2 was used for the calculation of sensitivity and specificity (Table 2.3). The GDS-3A had a sensitivity of 29.3% (21.4–38.1) and a specificity of 88.5% (84.4–91.8) in the DANTE Study, and 32.8% (24.5–41.1) and 92.6% (90.9–94.2), respectively, in the PROMODE Study. Correlation coefficients between the GDS-3A and the Apathy Scale were 0.42 in the DANTE Study and 0.39 in the PROMODE Study (both p-values<0.001). Coefficients remained largely similar after omitting either the first,

second or third item of the GDS-3A. Stratified analyses according to age, gender, cognitive function, presence of cardiovascular disease, and level of education rendered largely similar test characteristics in both studies (data not shown).

Table 2.3 Presence of apathy according to the GDS-3A and the Apathy Scale in the DANTE Study and the PROMODE Study

DANTE		**Apathy Scale ≥14**		
		Positive	Negative	
GDS-3A ≥2	Positive	36	35	71
	Negative	87	269	356
		123	304	427
Sensitivity	29.3% (21.4 - 38.1)			
Specificity	88.5% (84.4 - 91.8)			
LR+	2.54 (1.68 - 3.85)			
LR-	0.80 (0.71 - 0.90)			
PROMODE		**Apathy Scale ≥14**		
		Positive	Negative	
GDS-3A ≥2	Positive	40	74	114
	Negative	82	922	1004
		122	996	1118
Sensitivity	32.8% (24.5 - 41.1)			
Specificity	92.6% (90.9 - 94.2)			
LR+	4.41 (3.15 - 6.17)			
LR-	0.73 (0.64 - 0.82)			

Data are presented as numbers, percentages with 95% confidence intervals, or likelihood ratios with 95% confidence intervals.

GDS, Geriatric Depression Scale; LR, likelihood ratio

Discussion

In our study investigating the applicability of the GDS-3A in research settings, the GDS-3A only moderately discriminated between presence and absence of clinically relevant apathy in two populations of older persons, when using the Apathy Scale as reference standard. Using a cut-off of ≥2 for presence of apathy according to the GDS-3A, sensitivity compared to the Apathy Scale was 29.3% in the DANTE Study and 32.8% in the PROMODE study, whereas in both studies specificity was high (88.5% and 92.6%, respectively).

To the best of our knowledge, our study is the second to report epidemiological test characteristics for the GDS-3A, and the first to do so in two large cohorts of older persons with a wider age range. The likelihood ratios for the GDS-3A scores increased with increasing test scores in both studies, but poorly discriminated for

scores of one or two (1.53 and 1.96 in the DANTE Study, respectively, and 1.56 and 4.32 in the PROMODE Study). Although a score of three had a moderately high likelihood ratio in both studies (5.36 in the DANTE Study and 5.44 in the PROMODE Study), the number of participants in this category was very low in both studies, limiting power for analyses. Therefore we decided to use a cut-off of ≥2 for calculations of test characteristics in these populations, with modest corresponding likelihood ratios because of a low sensitivity and high specificity. In both the DANTE Study and the PROMODE Study the GDS-3A scores moderately but significantly correlated with Apathy Scale scores and the correlation did not depend on the performance of a single item.

A possible explanation for the moderate performance of the GDS-3A is that, although interviewer-administered, it records self-reported symptoms. The Apathy Scale however, is a semi-structured interview allowing the interviewer to incorporate his or her own clinical judgement and information obtained from proxies. Since disease awareness might be low in apathy [1], this difference might explain the low sensitivity of the GDS-3A. Although lack of self-awareness might at least partly explain the low sensitivity of the GDS-3A, our findings in the DANTE Study and the PROMODE Study contrasts with findings of Van der Mast *et al*. Using data from the Leiden 85-plus Study, they reported a sensitivity of 68.6% using the same cut-off values for both the GDS-3A and the Apathy Scale[14]. The difference in test characteristics might be explained by a higher prevalence of apathy according to the Apathy Scale in the Leiden 85-plus study, which was present in 51 out of 117 participants (43.6%) and might be due to the much higher age in the Leiden 85-plus Study. It is increasingly recognized that also sensitivity and specificity may vary across patient populations[30, 31]. For example with a lower disease prevalence, there may be more patients with less severe symptoms, and sensitivity can be lower[32].

In contrast to the population-based Leiden 85-plus Study, participants from both our studies were selected for participation in clinical trials, were on average younger, had better cognitive function, higher level of education and better cardiovascular health (the latter information only available in the DANTE Leiden Study). However, stratified analyses showed that aforementioned characteristics did not explain the differences in findings between our current study and the Leiden 85-plus Study.

Besides other, currently unmeasured, patient characteristics, differences in diagnostic accuracy might also be artificially caused by our use of the Apathy Scale, an imperfect reference standard[12, 33]. The Apathy Scale was developed in patients with Parkinson's disease[28] and showed good interrater reliability (r=0.81), test-retest reliability (r=0.90), and good internal consistency (Cronbach's α=0.76). Test characteristics for a cut-off of ≥14 compared to a clinical diagnosis of apathy were calculated in 12 patients (sensitivity 66%, specificity 100%). The only other study on psychometric properties of the Apathy Scale reported fair internal consistency

(Cronbach's α=0.69)[34]. Although data on the performance of the Apathy Scale in other populations is scarce, the questionnaire is derived from the well-validated Apathy Evaluation Scale (AES)[12, 35]. The Apathy Scale is shorter and has the possibility to combine information from the patient, informant and clinician, making it a more favourable instrument. Even so, these imperfect characteristics of our reference standard may underlie the moderate performance of the GDS-3A in our study. However, it must be emphasized that the same reference standard was used in the Leiden 85-plus Study, making results comparable for the purpose of this study. Moreover, if reference standard misclassification would explain differences in sensitivity and specificity, a pattern of higher sensitivity and lower specificity with increasing disease prevalence would be observed[33]. As this was not consistently found for the DANTE Study, PROMODE Study and Leiden 85-plus Study, it is less likely that reference standard misclassification explains the variation in sensitivity and specificity across the different studies.

Strengths of this study include the use of two relatively large sized, well-defined samples of older persons and very few missing data on the GDS-3A and Apathy Scale, implying a low risk of validation bias. Furthermore, the research protocols for the DANTE Study and the PROMODE Study were designed similarly with regard to administering the questionnaires, which contributes to comparability of results. However, there are several limitations of this study that need to be taken into account when interpreting the results. First, it is important to state that the current study was not designed to assess added diagnostic value, but is a test accuracy study aiming to investigate the applicability of the GDS-3A in research settings. Second, only 19 (4.4%, DANTE Study) and 10 (0.89%, PROMODE Study) of the participants had GDS-3A scores of three. Although numbers were too low to calculate valid diagnostic test characteristics for this cut-off in our study populations, increasing the cut-off for apathy might yield higher specificity but even lower sensitivity. This may be favoured in certain research settings, depending on the aim of the study. Third, the interviewers administering the Apathy Scale were not formally blinded for the GDS-3A scores, which could have led to information bias. Nonetheless, since the GDS-3A questions were incorporated in the GDS-15 questionnaire and our current aim was not the primary aim of the studies, we do not expect different results with a blinded study design. Furthermore, apathy can occur as a symptom of depression and as a syndrome in its own right[10]. As no formal diagnosis of depression was available in either study, we were not able to differentiate between apathy and depression. However, the GDS-3A items were identified as measuring apathy by several studies on construct validity[21-23] as well as an expert panel installed by Van der Mast *et al*.[14]. We therefore deem it justified using these items as a measure for apathy. Last, both the DANTE and PROMODE participants were selected for clinical trials, limiting generalizability of the study results.

The main premise of this study was to assess the applicability of the GDS-3A in research settings. Given the moderate likelihood ratios in both the DANTE and PROMODE Study, our results suggest that the GDS-3A is not a useful tool in clinical practice to screen for presence of apathy. However, the GDS-3A may still be a useful scale in research, depending on the aim of the study. Because of its low sensitivity regardless of the cut-off used, the GDS-3A will not be suitable to determine the prevalence of apathy in specific populations. In studies focussing on potential risk and prognostic factors however, it can still be a useful instrument as long as it can be assumed that the misclassification is non-differential. If so, effect sizes will be biased towards the null, both when the GDS-3A is used as a measure of outcome and determinant[36]. Furthermore, the higher the prevalence of apathy in a population, the smaller the bias will be[36], making the GDS-3A better suited for research in older populations.

In conclusion, our results from two large study cohorts show that the GDS-3A is only very moderately accurate in discriminating between presence and absence of clinically relevant apathy in older persons. Although we think it is therefore a less favourable screening tool for clinical practice, the GDS-3A can still be useful in research if no other measurement of apathy is available. Because of the non-differential misclassification, and thus dilution of effect, the GDS-3A is preferably used in large studies. Especially for studies among older people, with long follow-up, the GDS-3A might be attractive to study risk factors and prognostic factors for apathy, since it is unlikely that these earlier studies used a validated questionnaire. However, since it becomes increasingly clear that apathy is an important and useful endpoint in studies among older people, future studies should use a more valid instrument. In all instances, caution has to be taken in interpreting negative findings as evidence for absence of an association.

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Chapter 3

High sensitivity cardiac troponin T and neurocognitive functioning in the oldest old: the Leiden 85-plus Study

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Abstract

Background: Impaired cardiac function has been related to accelerated cognitive decline in late-life and may also be associated with neuropsychiatric symptoms such as depression and apathy.

Objective: To investigate whether higher levels of high sensitivity cardiac troponin T (hs-cTnT), a sensitive marker for myocardial injury, are associated with worse neurocognitive function in the oldest old.

Methods: In 455 participants of the population-based Leiden 85-plus Study, hs-cTnT was measured at 86 years. Cognitive function was measured annually during four years with the Mini Mental State Examination (MMSE). Symptoms of apathy were measured with the Geriatric Depression Scale (GDS)-3A, a 3-item subscale of the GDS-15, and depressive symptoms with the remaining 12 GDS-12D items.

Results: Participants in the highest gender-specific tertile of hs-cTnT had a 2.0-point lower baseline MMSE score than participants in the lowest tertile (95% confidence interval (CI) (95% CI 0.73-3.3), and had a 0.58-point steeper annual decline in MMSE during follow-up (95% CI 0.06-1.1). The associations remained after adjustment for sociodemographic and clinical characteristics, and after excluding those without a history of overt cardiac disease. Hs-cTnT was not related to symptoms of apathy at baseline, or during follow-up. At baseline, higher hs-cTnT was inconsistently related to depressive symptoms in the different models. During follow-up, there was no association between hs-cTnT and depressive symptoms.

Conclusion: In a population-based sample of the oldest old, higher levels of hs-cTnT were associated with worse cognitive function and faster cognitive decline, independently of a history of overt cardiac disease. This could mean that hs-cTnT is a marker for subclinical vascular damage. Hs-cTnT may be a more specific marker for cognitive decline than for symptoms of apathy and depression.

Introduction

Cardiac troponin T (cTnT) is a protein regulating the calcium-mediated actin and myosin interaction in cardiac myocytes[1]. Within hours after myocardial ischemia, blood levels of cTnT are markedly increased. Hence, a high level of serum cTnT is a clinical marker for acute myocardial ischemia and is therefore widely used in diagnosing acute myocardial infarction[2]. Recently, a high sensitivity (hs) assay for cTnT has become available for accurate measurement of concentrations below the clinical cut-off for myocardial infarction. In this range, higher levels of hs-cTnT in patients with heart failure[3, 4], renal failure[5] and acute pulmonary embolism[6], are related to worse disease-specific prognosis and increased mortality. Moreover, it has been shown in middle-aged and older community-dwelling persons without cardiovascular disease, that a graded increase in levels of cTnT is associated with cardiac events and mortality[7-9]. There is also a growing body of evidence that people with higher levels of hs-cTnT have a higher risk of non-cardiac adverse health outcomes such as stroke[10-12].

People with cardiovascular disease are at increased risk for cognitive decline and dementia[13-16]. Hence, higher levels of hs-cTnT, reflecting higher degrees of cardiac injury, may also be associated with accelerated cognitive decline and dementia. However, the available evidence on the relation between higher levels of hs-cTnT and adverse brain outcomes mainly comes from middle-aged and younger-old study populations[10-12]. It remains unclear whether in the rapidly expanding populations of very old people elevated levels of hs-cTnT associate with accelerated cognitive decline. Changes in hs-cTnT levels may also relate to cognitive function in those older persons without a history of overt cardiac disease, potentially through subclinical microvascular damage. As of yet, the association between hs-cTnT and symptoms of apathy and depression, two frequent neuropsychiatric symptoms in older persons[17], has not been studied.

In this study of a population-based sample of the oldest old, we aimed to investigate whether higher levels of hs-cTnT are associated with worse baseline cognitive function and accelerated cognitive decline. Further, we assessed whether an association between hs-cTnT and cognitive function was also present in those without a history of overt cardiac disease. As a secondary aim, we investigated the cross-sectional and longitudinal associations between hs-cTnT on the one hand, and symptoms of apathy and depression on the other hand.

Methods

Design and participants

The design and recruitment procedure of the Leiden 85-plus Study have been described in detail elsewhere[18]. In brief, the Leiden 85-plus Study is a prospective population-based cohort study of inhabitants of Leiden, the Netherlands, who reached the age of 85 years between 1997 and 1999. No other eligibility criteria were applied. The response rate was 87% and 599 participants were enrolled. Data was collected annually during home visits. Since hs-cTnT was determined at the age of 86 years, we considered this age as the baseline measurement for our current study. The 455 participants with complete data on Mini Mental State Examination (MMSE), hs-cTnT levels and covariates at the age of 86 were selected for our main analysis. The medical ethical committee of the Leiden University Medical Center approved the Leiden 85-plus Study, and all participants gave informed consent.

Measurement of high sensitivity cardiac troponin T

Hs-cTnT was measured from EDTA plasma using an electrochemiluminiscence immunoassay on a Roche Modular Analytics E170. The high-sensitivity assay has a detection limit of 3 ng/L and a 99th percentile cut-off of 14 ng/L. Because the Elecsys Troponin T hs assay used had a coefficient of variance (CV) of 10.38% at a hs-cTnT concentration of 10.0 ng/L, the assay was able to differentiate reasonably well at lower concentrations. For three participants with levels below the detection limit, hs-cTnT levels were set at 1.5 ng/L.

Measurement of cognitive function

Cognitive function was assessed with the MMSE at the age of 86 and then annually up until the age of 90[19]. The MMSE ranges from 0 - 30 points with lower scores indicating worse cognitive function.

Measurement of symptoms of apathy and depression

Depressive symptoms were assessed with the Geriatric Depression Scale-15[20]. A subscale of three items ((1) "Have you dropped many of your activities and interests?" (2) "Do you prefer to stay at home, rather than going out and doing new things?", and (3) "Do you feel full of energy?") was used to measure symptoms of apathy[21, 22]. This subscale, the GDS-3A, ranges from 0-3 with higher scores indicating more symptoms of apathy. The remaining 12 items of the GDS-15 were used to measure depressive symptoms. This subscale, the GDS-12D, ranges from 0-12 with higher scores indicating more symptoms of depression.

Demographic and clinical characteristics

Socio-demographic characteristics, smoking status and use of alcohol in glasses per week were assessed (at the age of 85) during a face-to-face interview. Level of education was specified in eight categories ranging from no education to an obtained university degree. As a measure of income, it was registered whether an individual received state pension only or had additional pension or income. All other parameters were obtained at the age of 86. Body Mass Index (BMI) was calculated as the weight in kilograms divided by the square of length in meters (kg/m^2). Blood pressure was measured twice in seated position with a mercury sphygmomanometer during home visits. The average of the two measurements was used in the analyses. Serum creatinine (µmol/L) and total cholesterol (mmol/L) were measured.

Information on the participant's medical history was obtained from their general practitioner (GP) or, in case of institutionalization, from their treating physician. Information on the use of medication was obtained from pharmacist records or, in case of institutionalization, from questionnaires filled out by the treating physician. A history of angina pectoris or heart failure was obtained from the GP or treating physician. A history of myocardial infarction was established when it was either reported by the GP or treating physician, or recorded as such on electrocardiograms (ECG) at the age of 85 or 86 using automated Minnesota coding (Code 1-1 or 1-2 excluding 1-2-8). The presence of atrial fibrillation was determined using the ECG at age 86 (Minnesota Code 8-3-1). The ECGs were recorded on a Siemens Sicard 440 (Erlangen, Germany) and were transmitted to the ECG Core Laboratory in Glasgow Royal Infirmary. A history of overt cardiac disease was defined as having either a history of myocardial infarction, angina pectoris, atrial fibrillation on ECG, or heart failure.

Statistical analysis

Data are presented as number (percentage), mean (±standard deviation, SD) or median (interquartile range, IQR) when appropriate. Demographic and clinical characteristics were compared between groups of lower, middle and higher levels of hs-cTnT according to gender-specific tertiles. Gender-specific tertiles were used because levels of hs-cTnT are gender-dependent[7]. P-values for linear trend were calculated with Pearson's Chi-square tests for categorical variables and analysis of variance (ANOVA) for normally distributed continuous variables. To test differences between the highest and lowest tertiles of hs-cTnT, ANOVA was used.

The distribution of hs-cTnT was skewed to the right and natural log-transformed (ln) hs-cTnT levels were used in the analyses. Linear regression analyses were used to calculate beta coefficients (β) per unit increase in ln-hs-cTnT with 95% confidence interval (CI) and p-values for the cross-sectional association between hs-cTnT on the one hand and MMSE, GDS-3A, and GDS-12D scores on the other

hand. The annual change in cognitive function for each participant was determined by calculating the beta (β) for the change in MMSE per individual per year, thus making optimal use of all available data during follow-up. Linear regression analyses were used to assess the longitudinal association between hs-cTnT and the annual change in MMSE. The longitudinal association between hs-cTnT and both GDS-3A and GDS-12D scores was assessed in participants without symptoms of apathy and depression at baseline[22]. We used linear mixed models for these analyses because, unlike the MMSE, these scores do not necessarily gradually deteriorate over time.
First, a crude analysis was performed (model 1). In model 2, we adjusted for gender, level of education and serum creatinine levels as these factors could confound the association between hs-cTnT and cognitive function. To assess whether the associations between hs-cTnT and measures of cognitive function were independent of sociodemographic and clinical characteristics including cardiovascular risk factors, in model 3 we additionally adjusted for income, alcohol use in glasses per week, history of smoking, history of diabetes, history of hypertension, systolic and diastolic blood pressure, BMI, total cholesterol levels, the use of antihypertensive medication, use of statins and the use of vitamin K antagonists. All analyses for the GDS-3A were also adjusted for GDS-12D scores. For analyses on cognitive function, all longitudinal analyses were adjusted for the baseline MMSE scores.
To assess whether the association between hs-cTnT and neurocognitive function depended on the presence of a history of overt cardiac diseases only, we repeated the cross sectional and longitudinal analyses of model 3 in a series of restricted samples. First, we excluded participants with a history of myocardial infarction, then those with a history of angina pectoris, then those with atrial fibrillation, and then those with a history of heart failure, allowing us to assess the effect of each of these individual cardiac diseases. As a next step, we excluded all participants with any history of the aforementioned cardiac diseases to assess whether higher levels of hs-cTnT associated with neurocognitive function in participants free from any history of overt cardiac disease. Additionally, we excluded participants with a history of stroke at baseline.
All analyses were performed using SPSS statistical software (SPSS for Windows, version 20, SPSS Inc., Chicago, IL) and figures were made in GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA).

Results

Demographic and clinical characteristics

In the entire study population, the median level of hs-cTnT was 14.0 ng/L (10.0-22.0). Table 3.1 shows the characteristics of the study participants in three groups of

hs-cTnT. Participants in the highest tertile (n=164) had a lower level of education, and more often had a history of cardiovascular disease and diabetes than those in the middle (n=166) and lowest tertile (n=125). Diastolic blood pressure and total serum cholesterol were lower in participants in the highest tertile of hs-cTnT, while serum creatinine levels were higher.

Table 3.1 Comparison of participant characteristics in gender-specific tertiles of hs-cTnT at the age of 86 (n=455)

	Lowest tertile (n=164)	**Middle tertile (n=166)**	**Highest tertile (n=125)**	**p-value[a]**
No or only basic education	89 (54)	109 (66)	82 (66)	0.04
Low income (state pension only)[b]	26 (16)	25 (15)	21 (17)	0.86
History of overt cardiac disease				
myocardial infarction[c]	15 (9)	35 (21)	27 (22)	0.004
angina pectoris[d]	22 (13)	37 (23)	30 (24)	0.02
atrial fibrillation[e]	12 (7)	20 (12)	23 (19)	0.004
heart failure[f]	17 (10)	22 (13)	26 (14)	0.01
History of stroke[g]	12 (7)	21 (12)	12 (10)	0.47
History of diabetes	20 (12)	19 (11)	34 (27)	0.001
History of hypertension	59 (36)	64 (39)	52 (42)	0.33
Use of antihypertensive medication	49 (30)	76 (46)	51 (41)	0.04
Use of vitamin K antagonists	3 (2)	8 (5)	7 (6)	0.09
Smoking status				
current	24 (15)	25 (15)	19 (15)	0.89
former	74 (45)	77 (46)	67 (54)	0.17
Use of alcohol	84 (51)	77 (46)	66 (53)	0.86
Number of glasses of alcohol/week	0.4 (0.0-7.0)	0.0 (0.0-4.0)	0.3 (0.0-4.8)	0.46
Body mass index (kg/m^2)	27.2 (4.3)	27.4 (4.8)	26.9 (4.5)	0.70
Systolic blood pressure (mmHg)	157 (16)	157 (19)	154 (22)	0.18
Diastolic blood pressure (mmHg)	77 (9)	77 (9)	73 (9)	0.001
Total cholesterol (mmol/L)	5.6 (1.0)	5.6 (1.1)	5.4 (1.1)	0.05
Serum creatinine (µmol/L)	90 (18)	96 (20)	117 (55)	<0.001

Data are presented as number with percentage or as mean with standard deviation

Ranges of tertiles men: lowest ≤14 ng/L, middle 15-23 ng/L, highest ≥24 ng/L. Women: lowest ≤10 ng/L, middle 11-18 ng/L, highest ≥19 ng/L

a: p-value for linear trend

b: n=4 missings for income

c: n=1 missings for myocardial infarction

d: n=4 missings for angina pectoris

e: n=4 missings for atrial fibrillation

f: n=1 missings for history of heart failure

g: n=2 missings for stroke

Abbreviations: hs-cTnT, high sensitivity cardiac troponin T

Hs-cTnT and cognitive function at baseline and during follow-up

Figure 3.1 graphically shows the mean unadjusted MMSE scores in tertiles of hs-cTnT from the age of 86 to 90. At baseline, participants in the highest tertile of hs-cTnT had a 2.0-point lower MMSE score than participants in the lowest tertile (95% CI 0.73 to 3.3, p=0.002).

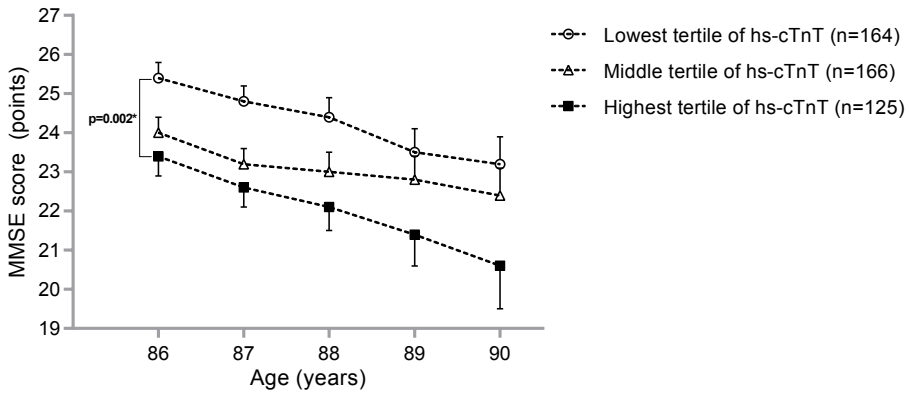

Figure 3.1 MMSE score from age 86 to 90 years in gender-specific tertiles of hs-cTnT

Data points represent unadjusted means with standard errors.
*p-value for mean difference between lowest and highest tertile at baseline (mean difference 2.0 point).
Numbers in lowest tertile: age 86, n=164; age 87, n=153; age 88, n=139; age 89, n=126; age 90, n=113
Numbers in middle tertile: age 86, n=166; age 87, n=153; age 88, n=144; age 89, n=127; age 90, n=111
Numbers in highest tertile: age 86, n=125; age 87, n=102; age 88, n=81; age 89, n=59; age 90, n=43
Abbreviations: MMSE, Mini Mental State Examination; hs-cTnT high sensitivity cardiac troponin T.

Table 3.2 shows the different models for the cross-sectional and longitudinal relation between hs-cTnT and MMSE score. During follow-up, participants in the highest tertile of hs-cTnT had a 0.58-point steeper annual decline in MMSE compared to participants in the lowest tertile (95% CI 0.06 to 1.1, p=0.03). The estimates for the relation between higher levels of hs-cTnT and both lower baseline MMSE score and a steeper annual decline on the MMSE remained similar in model 2 and model 3. Participants in the highest tertile were more likely to have less follow-up measurements (Supplementary Table S3.1).

Association between hs-cTnT and cognitive function in participants without a history of overt cardiac disease

Figure 3.2 shows the results from the analyses restricted to those participants without a history of myocardial infarction, angina pectoris, atrial fibrillation, and

heart failure. Estimates for the relation between hs-cTnT and MMSE remained similar for both the cross sectional and the longitudinal analyses, also when all 202 participants with any of the mentioned cardiac diseases were excluded.
Additional sensitivity analyses excluding those with a history of stroke at baseline showed similar results as in the entire sample (data not shown).

Table 3.2 Cross-sectional and longitudinal relation between hs-cTnT and (change in) MMSE scores

	Lowest tertile	Middle tertile	Highest tertile	β (SE)	95% CI	p-value[a]
MMSE						
Cross-sectional						
Model 1	25.4 (0.43)	24.0 (0.43)	23.4 (0.49)	-1.1 (0.44)	-2.0 to -0.25	0.01
Model 2	25.4 (0.42)	24.3 (0.42)	23.3 (0.50)	-1.6 (0.48)	-2.5 to -0.65	0.001
Model 3	25.8 (1.42)	24.4 (1.39)	24.0 (1.42)	-1.8 (0.46)	-2.7 to -0.87	<0.001
Annual change						
Model 1	-0.80 (0.17)	-1.22 (0.17)	-1.38 (0.21)	-0.62 (0.18)	-0.98 to -0.26	0.001
Model 2	-0.90 (0.17)	-1.32 (0.17)	-1.44 (0.23)	-0.56 (0.21)	-0.97 to -0.16	0.006
Model 3	-0.79 (0.61)	-1.23 (0.60)	-1.38 (0.62)	-0.62 (0.21)	-1.04 to -0.20	0.004

Numbers in the three gender-specific tertiles represent mean scores and mean annual change with SE

a: β, SE, 95% CI, and p-value calculated with linear regression with log-transformed hs-cTnT levels as the continuous determinant and the (annual change in) MMSE score as continuous outcome measures. All longitudinal analyses were adjusted for baseline MMSE scores

Model 1: crude

Model 2: adjusted for gender, level of education in eight sub groups, and serum creatinine

Model 3: adjusted for gender, level of education in eight sub groups, income, alcohol use in glasses/week, serum creatinine, former smoking status, body mass index, total cholesterol, systolic blood pressure, diastolic blood pressure, history of hypertension and history of diabetes, use of antihypertensive medication, use of statins, and use of vitamin K antagonists

Abbreviations: hs-cTnT, high sensitivity cardiac troponin T; MMSE, Mini Mental State Examination β, beta; SE, standard error; CI, confidence interval

The association between hs-cTnT and symptoms of apathy and depression

Levels of hs-cTnT were not associated with GDS-3A scores at baseline or during follow-up (data not shown). Adjusting for sociodemographic and clinical characteristics in model 2 and 3 did not change this association (data not shown), nor did excluding those with a history of overt cardiac disease (Supplemental Figure S3.1A+B).
In the cross-sectional analyses, hs-cTnT was not related to depressive symptoms in model 1 (data not shown). Participants in the highest gender-specific tertile of hs-cTnT had higher scores on the GDS-12D than those in the middle tertile in model 2 (1.72 vs 1.17 points, p=0.046) and model 3 (1.42 vs. 0.85 points, p=0.045).

When we analyzed hs-cTnT as a continuous determinant, the association between higher levels of hs-cTnT and higher GDS-12D scores was significant in the minimally adjusted model 2 (ß=0.46, 95% CI 0.06 to 0.86, p=0.02), but not in the fully adjusted model 3 (ß=0.27, -0.12 to 0.66, p=0.17). When excluding participants with overt cardiac disease, higher levels of hs-cTnT were associated with higher GDS-12D scores in those without a history of angina pectoris and in those without a history of heart failure (Supplemental Figure S3.1C). No longitudinal association between hs-cTnT and GDS-12D scores was found in model 1 or 2 (data not shown), nor in model 3 (Supplemental Figure S3.1D). Restricting the analyses to those participants without a history of overt cardiac disease did not change the associations (Supplemental Figure S3.1D).

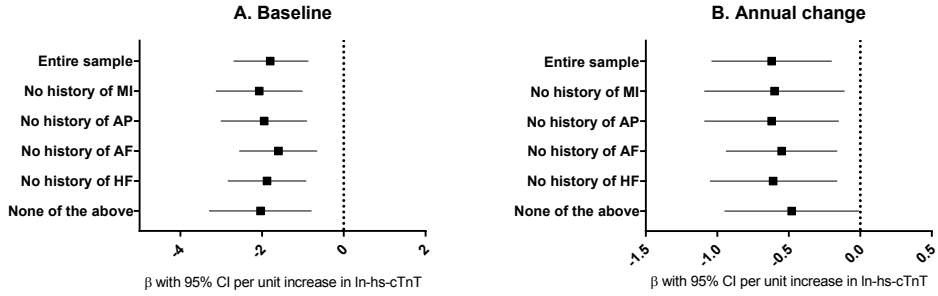

Figure 3.2 Cross sectional and longitudinal relation between hs-cTnT and MMSE score according to history of cardiac disease

β with 95% CIs were calculated with linear regression with log-transformed hs-cTnT levels as the continuous determinant and MMSE score as a continuous outcome variable. All analyses were adjusted for gender, level of education in eight sub groups, income, alcohol use in glasses/week, serum creatinine, former smoking status, body mass index, total cholesterol, systolic blood pressure, diastolic blood pressure, history of hypertension and history of diabetes, use of antihypertensive medication, use of statins, and use of vitamin K antagonists (model 3).

Abbreviations: β, beta, 95% CI, 95% confidence interval; (ln)-hs-cTnT, (log-transformed) high sensitivity cardiac troponin T; MMSE, Mini Mental State Examination.

Numbers in the different groups: entire sample: n=455, no history of myocardial infarction (MI): n=377, no history of angina pectoris (AP): n=362, no history of atrial fibrillation (AF): n=396, no history of heart failure (HF): n=389. None of the above: n=253.

Discussion

In a population-based sample of the oldest old, people with higher levels of hs-cTnT had worse cognitive function at baseline and a faster annual cognitive decline during 4-years follow-up, independently of cardiovascular risk factors and a history of overt cardiac disease. As expected in this age group, those with the highest

hs-cTnT levels were more likely to have fewer follow-up MMSE measurements, due to mortality[23]. Despite this, a greater cognitive decline was observed in this group. This might suggest an underestimation of the reported association, since cognitive decline is associated with increased mortality, even in the absence of dementia [24].

To date, few studies have investigated the relation between hs-cTnT and cognitive function, and, to the best of our knowledge, ours is the first to do so in the oldest old. Our findings are in line with results from the Atherosclerosis Risk In Communities (ARIC) study, demonstrating that higher levels of hs-cTnT were associated with worse baseline cognitive function and incident dementia, in community-dwelling participants aged around 65, without coronary artery disease, heart failure or stroke[25]. Additionally, a recent study among older persons (mean age 75 years) with a high burden of vascular diseases (coronary, cerebral or peripheral) or risk factors, found higher levels of hs-cTnT to be associated with worse cognitive function and steeper cognitive decline[26]. In contrast, another study among memory clinic patients aged around 70, reported that only in patients with cerebrovascular disease, higher levels of hs-cTnT were related to cognitive impairment and dementia[27] which suggests a role particularly for vascular brain pathologies in the relation between hs-cTnT and cognitive function. In light of other findings in the literature, our study adds that the relation between higher levels of hs-cTnT and worse cognitive function is also found in the oldest old, independently of the presence of cardiovascular risk factors and a history of overt cardiac disease. It is an important finding that the direction of the effect is the same as in younger populations, since several other conventional (cardiovascular) risk factors and markers such as blood pressure[28] and serum cholesterol[29, 30], show inverse predictive associations in the oldest old people. This might suggest that the mechanisms involved in the relation between hs-cTnT and cognitive decline are not changing over age.

Several explanations can be given for the finding of an association between higher levels of hs-cTnT and worse cognitive function. First, cardiovascular risk factors, impaired kidney function and cardiac diseases may lead to both higher levels of hs-cTnT and worse cognitive function. To address this, we adjusted our analyses for cardiovascular risk factors and kidney function, which did not change our results. Moreover, even when we excluded those participants with a history of overt cardiac disease, higher levels of hs-cTnT were still associated with worse cognitive function. Second, not only clinically overt but also microvascular coronary artery disease may cause elevated levels of hs-cTnT[8]. A study comparing non-ischemic heart failure patients with non-heart failure patients, demonstrated that the presence of coronary microvascular dysfunction was associated with an increased release of cTnT from the myocardium[31]. Since it has been shown that even subclinically reduced cardiac function is related to worse cognitive function[32], this may underlie our findings of an association of higher hs-cTnT and worse cognitive

function. Third, the independent association between higher levels of hs-cTnT and worse cognitive function could also imply that higher levels of hs-cTnT not only indicate microvascular coronary disease, but rather reflect a global microvascular disease including cerebral small vessel disease. Indeed, higher levels of hs-cTnT have not only been linked to overt adverse brain outcomes such as stroke[11, 12], but also to subclinical vascular brain abnormalities[33], which in turn predispose individuals to an increased risk of accelerated cognitive decline[34, 15]. In the current study, results remained similar after exclusion of participants with a history of myocardial infarction as well as stroke, which may suggest a role for subclinical vascular damage in the association between higher levels of hs-cTnT and worse cognitive function. Our findings support the notion that cardiac function (and cardiac biomarkers) are of importance for brain aging and cognitive decline[35-37]. Hs-cTnT may be a marker of microvascular coronary artery disease or global microvascular disease underlying processes of cognitive deterioration in older people. Future studies may provide insight into the role of (micro) vascular brain pathologies in the association between hs-cTnT and cognitive function. Besides mechanistic insights, combined with the findings in younger study populations, these results warrant future studies to investigate the added value of hs-cTnT to predict cognitive decline and potentially dementia[38, 39].

We found no association between hs-cTnT and symptoms of apathy at baseline and during follow-up. To the best of our knowledge, this is the first study to report this association. A previous report from the Leiden 85-plus Study was the first to use the GDS-3A as a measure for apathy and demonstrated an association between an increasing number of cardiovascular pathologies and incident apathy[22]. Combined with other studies showing an association between cardiovascular pathologies and apathy[40, 41], this has led to the concept of 'vascular apathy'. Thus, the lack of an association in our current study was in contrast to our hypothesis. Because of the low discriminative value of the GDS-3A in measuring apathy[21], it could be hypothesized that our study lacked the statistical power to detect an association with hs-cTnT.

This study is the first to investigate the association between hs-cTnT and depressive symptoms and we found an inconsistent relation between higher hs-cTnT and more depressive symptoms. Cross-sectionally, higher levels of hs-cTnT were related to more depressive symptoms in the entire sample, but only in the minimally adjusted model. In the crude and fully adjusted model, and in the longitudinal analyses, no association between continuous levels of hs-cTnT and depressive symptoms was found. Potentially these are chance findings or depend on the method of measuring depressive symptoms. More studies, preferably with larger study populations, are needed to elucidate the inconsistent relation between hs-cTnT and depressive symptoms.

Combined, these findings suggest that hs-cTnT could be a more specific marker for worse cognitive function and cognitive decline than for symptoms of apathy and depression in older persons.

Strengths of our study include the well-defined population-based sample of the oldest old, the annually repeated cognitive assessment and availability of detailed clinical information to evaluate the potential role of overt cardiac diseases. However, when interpreting these results, certain limitations of our study must be taken into account. First, in the Leiden 85-plus Study, no echocardiographies were performed at the baseline for this study. We therefore did not have a direct measure of cardiac function available, such as left ventricular ejection fraction or cardiac output, and had to approximate this using cardiac diseases. Additionally, neuroimaging data is not available to investigate the potential role of subclinical cerebrovascular damage in the relation between hs-cTnT and cognitive decline. Furthermore, because of the observational design and despite adjustments for sociodemographic and clinical characteristics as well as cardiovascular risk factors, there might still be residual confounding. Last, the MMSE is a broad measure of global cognitive function and does not cover all cognitive domains, nor does it ascertain the presence of dementia.

In conclusion, in a population-based sample of the oldest old, people with higher levels of hs-cTnT had worse cognitive function and a faster decline in cognitive function over time, independently of cardiovascular risk factors and a history of overt cardiac disease. Hs-cTnT may be a more specific marker for cognitive decline than for symptoms of apathy and depression.

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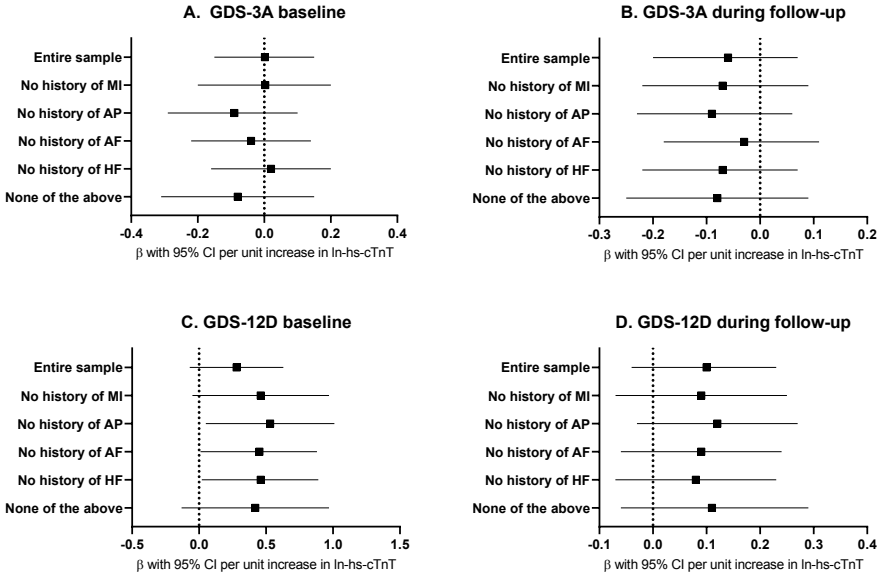
Supplementary material

Supplementary Table S3.1 Number of follow-up MMSE measurements in gender-specific tertiles of hs-cTnT at baseline

	Lowest (n=164)	**Middle (n=166)**	**Highest (n=125)**
Number of follow-up MMSE measurements (n, %)			
0	11 (7)	13 (8)	23 (19)
1	14 (9)	9 (5)	21 (17)
2	13 (8)	17 (10)	22 (18)
3	13 (8)	16 (10)	16 (13)
4	113 (69)	111 (67)	43 (34)

Numbers (percentages) represent number of follow-up measurements, starting at the age of 87 (maximum of 4 measurements)

Abbreviations: MMSE, Mini Mental State Examination, hs-cTnT denotes high sensitivity cardiac troponin T



Supplemental Figure S3.1 Cross sectional and longitudinal relation between hs-cTnT and GDS-3A and GDS-12D scores according to history of cardiac disease

β with 95% CIs were calculated with linear regression with log-transformed hs-cTnT levels as the continuous determinant and GDS sub scores as a continuous outcome variable. All analyses were adjusted for gender, level of education in eight sub groups, income, alcohol use in glasses/week, serum creatinine, former smoking status, body mass index, total cholesterol, systolic blood pressure, diastolic blood pressure, history of hypertension and history of diabetes, use of antihypertensive medication, use of statins, and use of vitamin K antagonists (model 3). Analyses for the GDS-3A were additionally adjusted for GDS-12D scores.

Abbreviations: β, beta, 95% CI, 95% confidence interval; (ln)-hs-cTnT, (log-transformed) high sensitivity cardiac troponin T; GDS, Geriatric Depression Scale.

Chapter 4

Lower blood pressure and apathy coincide in older persons with lower functional ability: the DANTE Study Leiden

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Abstract

Objective: To examine the association between blood pressure measures and symptoms of apathy and depression in older participants with various levels of functional ability.

Design: Cross-sectional study, using baseline data from the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) Study Leiden.

Setting: Primary care setting, the Netherlands.

Participants: Four hundred thirty community-dwelling participants aged 75 years and above.

Measurements: Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were measured during home visits. Symptoms of apathy and depression were assessed with the Apathy Scale and the Geriatric Depression Scale (GDS-15), respectively. Stratified linear regression was performed in participants with higher and lower functional ability according to the median of the Groningen Activity Restriction Scale.

Results: In participants with lower functional ability, each 10 mmHg lower SBP, DBP and MAP were associated with higher Apathy Scale scores (0.63, 0.92 and 0.94 points, respectively, all $P < 0.005$), but not with GDS-15 scores. In participants with higher functional ability blood pressure measures were not associated with Apathy Scale or GDS-15 scores.

Conclusion: In older participants with lower functional ability, lower blood pressure was associated with more symptoms of apathy, but not depression.

Introduction

Symptoms of apathy and depression are common in old age[1]. Apathy often occurs within the context of depression, but is also increasingly recognized as a distinct syndrome in which lack of motivation is a predominant feature[2].

Observational studies have shown inconsistent results for the relationship between blood pressure with symptoms of apathy and depression in old age. Cross-sectional associations have been found between higher blood pressure and symptoms of apathy[3, 4] and depression[5] in community dwelling older persons. Contradictory, other studies have found lower blood pressure to be cross-sectionally[6, 7] and longitudinally[8] associated with symptoms of depression. Heterogeneity of population characteristics may underlie the variety of study outcomes.

Older persons of a similar chronological age appear to be highly heterogeneous in their biological age and, accordingly, in their functional ability. There is increasing evidence that the clinical implications for blood pressure in old age depend on level of function ability. A prospective cohort study in the oldest old, showed that a lower, rather than a higher blood pressure predicted cognitive decline[9]. This relationship was most pronounced in those with pre-existing lower functional ability. Furthermore, in older persons with lower functional ability, a lower blood pressure has been associated with increased risk of stroke[10] and mortality[11,12]. These findings suggest that a lower blood pressure in older persons with lower functional ability may, possibly as a result of a dysfunctional vascular system, compromise cerebral perfusion with resulting adverse health outcomes[13]. It is unclear whether the relationship between blood pressure and symptoms of apathy and depression in older persons also depends on level of functional ability.

In the Discontinuation of ANtihypertensive Treatment in the Elderly (DANTE) Study Leiden, we recruited community-dwelling persons aged 75 years and above with mild cognitive dysfunction who were using antihypertensive medication and with a wide range of functional ability. This allowed us to examine cross-sectionally whether the association between blood pressure and symptoms of apathy and depression differs between older persons with lower and higher functional ability. We hypothesize that especially among older persons with a lower functional ability, a lower blood pressure is associated with more symptoms of apathy and depression.

Methods

Study design and participants

Data were obtained from the baseline assessment of the DANTE Study Leiden. This randomized controlled trial evaluates whether temporary discontinuation of antihypertensive medication in older participants with mild cognitive dysfunction improves cognitive and psychological functioning.

Participants (n=430), aged 75 years and above, were recruited from primary care practices in the Netherlands between May 2011 and July 2013. Participants were included when they had a Mini Mental State Examination (MMSE) score between 21 and 27, were on antihypertensive medication, and had a current systolic blood pressure (SBP) ≤160 mmHg (≤140 mmHg in case of diabetes mellitus (DM), peripheral arterial disease, or myocardial infarction (MI) or coronary reperfusion procedure >3 years ago). Exclusion criteria were: a history of stroke or transient ischemic attack (TIA), a recent (≤3 years) MI or coronary reperfusion procedure, current angina pectoris, cardiac arrhythmias, heart failure requiring antihypertensive medication, use of antihypertensive medication other than for hypertension, a clinical diagnosis of dementia or a limited life expectancy.

The DANTE Study Leiden was approved by the medical ethics committee of the Leiden University Medical Center and informed consent was obtained from all participants[14].

Assessment of blood pressure

SBP and diastolic blood pressure (DBP) were measured twice in all participants in the sitting position using a digital sphygmomanometer on the right arm, with two minutes between measurements. For the analyses, the mean value of the two measurements was used. The mean arterial pressure (MAP) was calculated as 1/3·(SBP)+ 2/3·(DBP) as a proxy for cerebral blood flow[15].

Assessment of apathy and depression

The presence of apathy was assessed with the Apathy Scale[16]. This semi-structured interview scale consists of 14 items (range 0-42 points), with higher scores indicating more severe apathy. A score ≥14 is indicative for the presence of clinically significant apathy[16]. The presence of depressive symptoms was assessed with the Geriatric Depression Scale (GDS)–15[17]. This questionnaire consists of 15 items (range 0-15 points) with higher scores indicating more severe depressive symptoms. A score ≥5 is indicative for the presence of clinically significant depressive symptoms[17].

Assessment of functional ability

The Groningen Activity Restriction Scale (GARS)[18] was used to examine functional ability. The GARS is an instrument to measure functional ability in activities of daily living (ADL, 11 items) and in instrumental activities of daily living (iADL, 7 items), with higher scores indicating lower functional ability (range 18-72 points).

Demographic and clinical characteristics

Demographic and clinical characteristics were collected from all participants using a standardized interview. Education was dichotomized at primary education (six years of schooling) and use of alcohol was dichotomized at 14 units/week. Medical history including use of medication was obtained for 426 participants from their general practitioner using structured questionnaires. To assess comorbidity, a set of chronic diseases was obtained, defined as DM, chronic obstructive pulmonary disease (COPD), Parkinson's disease, malignancy, and/or osteoarthritis[19, 20]. Furthermore, history of cardiovascular diseases (CVD) was assessed. Since patients with stroke or TIA were excluded from the DANTE Study Leiden, a history of CVD comprised MI or coronary reperfusion procedure >3 years ago or a history of peripheral arterial vascular disease. The MMSE score at inclusion was used as a measure of global cognitive functioning and the Stroop interference score (time to complete Stroop card 3 – ((time to complete Stroop card 1 + Stroop card 2)/2))[21] as a measure of executive cognitive functioning. Current use of psychotropic medication comprised antipsychotic and antidepressant therapy, as well as the use of benzodiazepines.

Statistical analysis

Demographic and clinical characteristics in participants with lower and higher functional ability are presented as numbers with percentages, means with standard deviations (± SD), or medians with interquartile ranges (IQR) when appropriate. Characteristics were compared using Pearson's Chi-squared tests for categorical variables, Student's t-tests for continuous independent variables with normal distribution, and non-parametric Mann-Whitney tests for continuous independent variables with non-normal distribution.

In the entire sample, the relationship between blood pressure measures and symptoms of apathy and depression was tested with multiple linear regression models. Unstandardized betas (β) and 95% confidence intervals (CI) were calculated per 10 mmHg increase in blood pressure measures. In the adjusted model we added age, gender, education, current smoking status, use of alcohol, history of CVD, number of chronic diseases, use of beta blockers, current use of psychotropic medication, GARS score, and MMSE score as covariates. Separately, we added the Stroop interference score to the adjusted model to explore the influence of executive functioning to our findings.

Interaction between level of functional ability (total GARS score dichotomized on the median score of 22) with blood pressure measures regarding symptoms of apathy and depression was tested by adding an interaction term in linear regression models. To further investigate whether this potential interaction effect of blood pressure measures with level of functional ability was driven by an impairment of iADL, ADL or both, we performed separate interaction analyses for the iADL and ADL subscales (dichotomized on the median scores of 9 and 13, respectively).
Stratified multiple linear regression analyses were performed in participants with lower (GARS score >22 points (median)) and participants with higher functional ability (GARS score ≤22), using blood pressure measures as continuous independent variables and the Apathy Scale and GDS-15 scores as continuous dependent variables. A sensitivity analysis was performed in participants without depressive symptoms according to a score of less than 2 points on a subscale of 12 items of the GDS-15, which solely indicates symptoms of depressed mood and dissatisfaction with life, rather than symptoms of apathy[3].
A p-value of <0.05 was considered significant. All analyses were performed with SPSS software (version 20.0 SPSS Inc., Chicago, IL).

Results

Demographic and clinical characteristics

Table 4.1 shows the demographic and clinical characteristics in strata of functional ability. Participants with a lower functional ability were older (83.1 (±4.9) years versus 79.7 (±3.5) years, p<0.001) and less often male (65 (31.1%) versus 105 (47.7%), p<0.001) in comparison to those with higher functional ability. Furthermore, participants with a lower functional ability were less educated, more often used psychotropic medication, more often had at least one chronic disease, had lower executive functioning and had more symptoms of apathy and depression.

Table 4.1 Characteristics of participants and by strata of functional ability (n=430)

	Lower functional ability[a] (GARS score >22, n=209)	Higher functional ability[a] (GARS score ≤22, n=220)	p-value
Demographics			
Age (years)	83.1 (±4.9)	79.7 (±3.5)	**<0.001**
Male	65 (31.1)	105 (47.7)	**<0.001**
Lower education (≤ 6 years)	85 (40.7)	58 (26.4)	**0.002**
Clinical characteristics			
Current smoking	20 (9.6)	19 (8.6)	0.74
Alcohol ≥14 units per week	16 (7.7)	28 (12.7)	0.08
History of CVD[b,c]	28 (13.6)	20 (9.1)	0.15
Presence of chronic diseases[b,d]	139 (67.5)	116 (53.0)	**0.002**
Use of antihypertensive medication[b]			
Beta blocker	83 (40.1)	89 (40.6)	0.91
Diuretic	109 (52.7)	119 (54.3)	0.73
ACE inhibitor or ARB	140 (67.6)	141 (64.4)	0.48
CCB	53 (25.6)	50 (22.8)	0.50
Use of psychotropic medication[b]	48 (23.2)	29 (13.2)	**0.008**
Benzodiazepines	26 (12.6)	21 (9.6)	0.33
Antidepressants	28 (13.5)	12 (5.5)	**0.004**
Antipsychotics	4 (1.9)	0 (0.0)	**0.04**
MMSE (points)	26.0 (25.0-27.0)	26.0 (25.0-27.0)	0.18
Stroop interference score (seconds)	33.0 (23.3-53.6)	29.0 (20.0-44.0)	**0.02**
Blood pressure			
Systolic (mmHg)	146.9 (±22.0)	148.5 (±21.0)	0.43
Diastolic (mmHg)	80.0 (±11.3)	82.0 (±10.5)	0.05
Mean arterial pressure (mmHg)	102.8 (±13.9)	104.2 (±12.5)	0.13
Neuropsychiatric measures			
Apathy Scale (points)	12.6 (±5.0)	10.2 (±4.1)	**<0.001**
≥14 points	82 (39.4)	42 (19.1)	**<0.001**
GDS-15 (points)	2.0 (1.0-3.0)	1.0 (0.0-2.0)	**<0.001**
≥5 points	32 (15.4)	13 (5.9)	**0.001**
Functional ability			
GARS (points)	28.0 (25.0-34.0)	19.0 (18.0-20.0)	
ADL (points)	16.0 (14.0-19.0)	11.0 (11.0-12.0)	
iADL (points)	13.0 (10.5-15.0)	7.0 (7.0-8.0)	

The data are presented as mean (±standard deviation), median (interquartile range) or number (percentage) where appropriate

The p-values are calculated for the difference between groups with higher and lower functional ability using the Students' t-test, Mann-Whitney test and the Pearson's Chi-squared test where appropriate

GARS = Groningen Activity Restriction Scale, CVD = cardiovascular disease, ACE = Angiotensin Converting Enzyme, ARB = Angiotensin Receptor Blocker, CCB=calcium channel blocker, MMSE = Mini Mental State Examination, mmHg = millimetres of mercury, GDS = Geriatric Depression Scale, ADL = activities of daily living, iADL = instrumental activities of daily living

Range of instruments: GARS 18-72, MMSE 0-30, Apathy Scale 0-42, GDS 0-15, ADL 11-44, iADL 7-28

a: 1 missing value on the GARS

b: Missing values: n=4 in group with higher functional ability and n=3 in group with lower functional ability

c: cardiovascular diseases comprise myocardial infarction or percutaneous coronary intervention or coronary artery bypass graft ≥ 3 years ago, or peripheral arterial disease

d: chronic diseases include diabetes mellitus, Parkinson's disease, chronic obstructive pulmonary disease, malignancy, and osteoarthritis

Association between blood pressure and symptoms of apathy and depression

In the entire population, lower blood pressure measures were associated with more symptoms of apathy in the adjusted model (SBP: β=-0.29, p=0.006, DBP: β= -0.24, p=0.23, MAP: β=-0.36, p=0.03), whereas only a lower systolic blood pressure was associated with symptoms of depression (β=-0.10, p=0.04).

In both the crude and adjusted model, significant interactions were present between SBP, DBP and MAP and the level of functional ability (total GARS score) regarding Apathy Scale scores (all p-values for interaction terms ≤0.005). Additional interaction analyses between blood pressure measures with iADL or ADL subscales of the GARS regarding Apathy Scale scores, showed that significant interaction was present for iADL, but not for ADL (data not shown). In contrast, no interaction was present between the blood pressure measures and the level of functional ability regarding GDS-15 scores.

Stratified analyses in Table 4.2 show that for participants with lower functional ability, a lower blood pressure was associated with higher Apathy Scale scores. In the adjusted model, for participants with lower functional ability each 10 mmHg lower SBP, DBP and MAP was associated with a 0.63 (p<0.001), 0.92 (p=0.003) and 0.94 (p<0.001) points higher score on the Apathy Scale, respectively. Additional adjustment for executive function did not essentially change these estimates. In participants with higher functional ability blood pressure measures were not associated with Apathy Scale scores. Furthermore, blood pressure measures were not associated with GDS-15 scores in either stratum of functional ability.

Figure 4.1 shows the association between blood pressure measures and the Apathy Scale and GDS-15 scores, dependent on the level of functional ability. The figure shows the opposite directions of the effect of blood pressure on symptoms of apathy in participants with lower and higher functional ability.

A sensitivity analysis of the association between blood pressure and symptoms of apathy among 302 participants without depressive symptoms, showed similar directions of effect and largely similar effect sizes for both strata of functional ability (data not shown).

Table 4.2 Mean Apathy Scale scores in groups of blood pressure measures, stratified by level of functional ability

	Lower functional ability (GARS score >22, n=209)					**Higher functional ability (GARS score ≤22, n=220)**				
	Systolic blood pressure (mmHg)					**Systolic blood pressure (mmHg)**				
	< 140	**140-160**	**> 160**			**< 140**	**140-160**	**> 160**		
	n=79	**n=74**	**n=56**	**Beta (95% CI)**	**p-value**	**n=83**	**n=75**	**n=62**	Beta (95% CI)	**p-value**
Crude model	14.1 (0.6)	11.6 (0.6)	11.9 (0.7)	-0.53 (-0.84 to -0.22)	**0.001**	9.9 (0.5)	9.9 (0.5)	10.9 (0.5)	0.20 (-0.06 to 0.46)	0.13
Adjusted model*	14.3 (0.6)	11.6 (0.6)	11.6 (0.7)	-0.63 (-0.94 to -0.32)	**<0.001**	9.9 (0.5)	10.0 (0.5)	10.6 (0.5)	0.13 (-0.14 to 0.40)	0.35
	Diastolic blood pressure (mmHg)					**Diastolic blood pressure (mmHg)**				
	< 80	**80-90**	**> 90**			**< 80**	**80-90**	**> 90**		
	n=104	**n=69**	**n=36**	**Beta (95% CI)**	**p-value**	**n=88**	**n=85**	**n=47**	**Beta (95% CI)**	**p-value**
Crude model	13.4 (0.5)	11.7 (0.6)	12.0 (0.8)	-0.76 (-1.36 to -0.16)	**0.01**	9.7 (0.4)	10.6 (0.4)	10.3 (0.6)	0.38 (-0.14 to 0.90)	0.15
Adjusted model*	13.6 (0.5)	11.8 (0.6)	11.3 (0.8)	-0.92 (-1.52 to -0.32)	**0.003**	9.6 (0.4)	10.7 (0.5)	10.3 (0.6)	0.48 (-0.05 to 1.01)	0.08
	Mean arterial pressure (mmHg)					**Mean arterial pressure (mmHg)**				
	<96.5	**96.5-108**	**>108**			**< 99**	**99-108**	**>108**		
	n=70	**n=71**	**n=68**	**Beta (95% CI)**	**p-value**	**n=74**	**n=72**	**n=74**	**Beta (95% CI)**	**p-value**
Crude model	14.0 (0.6)	12.2 (0.6)	11.7 (0.6)	-0.78 (-1.27 to -0.29)	**0.002**	9.4 (0.5)	10.6 (0.5)	10.5 (0.5)	0.37 (-0.07 to 0.80)	0.10
Adjusted model*	14.4 (0.6)	12.1 (0.6)	11.2 (0.6)	-0.94 (-1.43 to -0.45)	**<0.001**	9.4 (0.5)	10.6 (0.5)	10.4 (0.5)	0.34 (-0.10 to 0.79)	0.13

P-values were calculated using systolic and diastolic blood pressure and mean arterial pressure as continuous variables. Beta's represent change in Apathy Scale Score per 10 mmHg increase in blood pressure measures GARS = Groningen Activity Restriction Scale, mmHg = millimeters of mercury, CI = confidence interval. Range of instruments: GARS 18-72, Apathy Scale 0-42. *Adjusted for gender, age, education, current smoking, use of alcohol, history of cardiovascular disease, number of chronic diseases, use of psychotropic medication, use of beta blockers and Mini Mental State Examination score

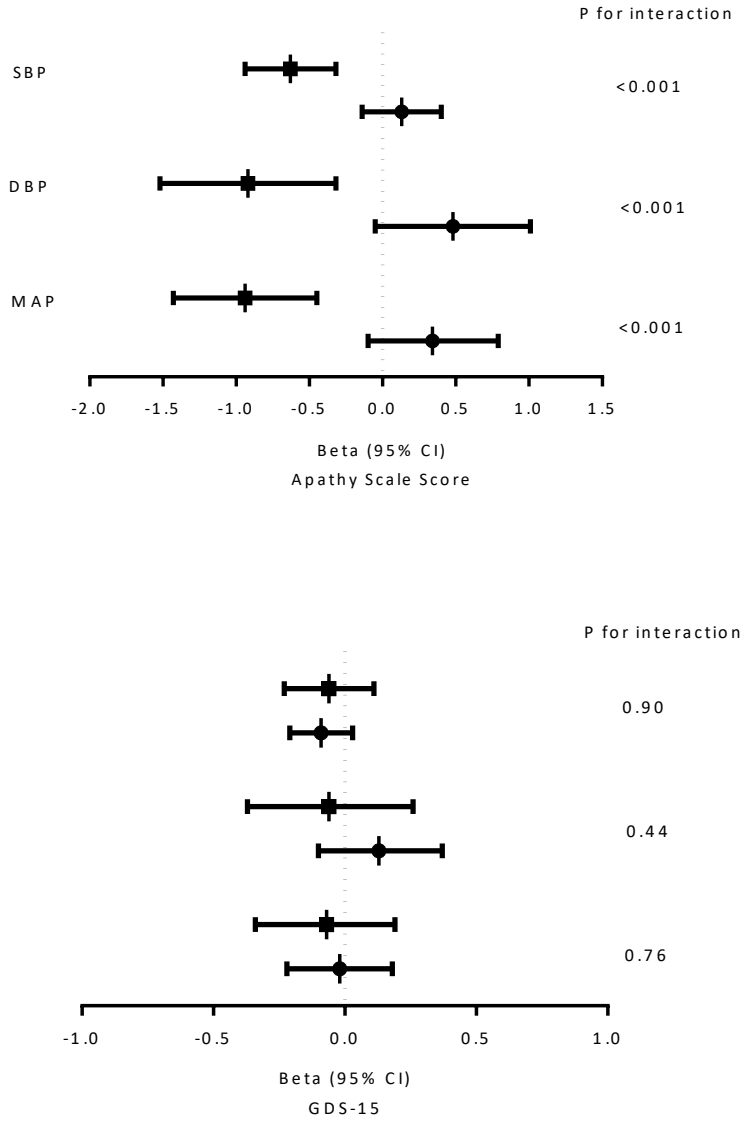

Figure 4.1 Association between blood pressure and symptoms of apathy and depression according to level of functional ability

Unstandardized beta's (95% CI) represent change in Apathy Scale or Geriatric Depression Scale (GDS)-15 score per 10 mmHg increase in blood pressure measures, dependent on level of functional ability. Lower functional ability was defined as Groningen Activity Restriction Scale (GARS) score >22 (■) (n=209) and higher functional ability as GARS score ≤22 (●) (n=220). Range GARS score: 18-72. Analyses were adjusted for gender, age, education, current smoking, use of alcohol, history of cardiovascular disease, number of chronic diseases, use of psychotropic medication, use of beta blockers and MMSE. SBP= systolic blood pressure, DBP= diastolic blood pressure, MAP= mean arterial pressure.

Discussion

In older persons with lower functional ability, a lower systolic, diastolic and mean arterial pressure were associated with more symptoms of apathy, but not with symptoms of depression.

Contradictory to our findings, two cross-sectional studies suggested a relationship between a higher blood pressure and apathy[3, 4]. However, these studies included community-dwelling older persons according to less stringent selection criteria, who were about 10 years younger than participants in our study. Furthermore, these studies did not consider functional ability as an effect modifier. Previous studies found a cross-sectional[6,7] and longitudinal association[8] for lower blood pressure and symptoms of depression. We found no such association in either stratum of functional ability. This discrepancy may be due to limited power, taking into consideration the low prevalence of symptoms of depression in our study population. However, we cannot exclude that lower blood pressure was truly not associated with symptoms of depression, but only with symptoms of apathy. It has been suggested before that apathy and depression have different risk factors and etiologies[19].

We found that interaction between the level of functional ability with various blood pressure measures regarding Apathy Scale score was present for iADL, but not for ADL. This may be explained by iADL being a more sensitive subscale to detect subtle changes in functional ability in our population with an overall high level of functional ability in comparison to the ADL subscale[18].

We are not able to make causal inference from our cross-sectional observational study, but we can speculate on explanations for our findings. First, lower blood pressure related symptoms of apathy in participants with lower functional ability may be due to better treatment of higher blood pressure in participants with more comorbid diseases (who are at risk for symptoms of apathy). However, blood pressure measures were not significantly lower in participants with lower functional compared to participants with higher functional ability. Second, lower blood pressure may not be causally related to symptoms of apathy in older persons with lower functional ability, but rather share a cause, such as cardiac dysfunction. Cardiac dysfunction can precede a lower blood pressure[22], lower functional ability[23] and symptoms of apathy[24]. However, persons with clinical heart failure were excluded from participation in our study. Moreover, participants with lower and higher functional ability had an equal proportion of history of cardiovascular disease. Additionally, the observed associations did not essentially change after adjustment for this factor. Third, incipient dementia may precede a lower blood pressure[25], functional impairment[26], and symptoms of apathy[27]. Although persons with dementia were excluded, participants with lower functional ability did have

a lower level of executive cognitive functioning compared to participants with higher functional ability. Nevertheless, the observed associations in this study did not essentially change after additional adjustment for executive function. Finally, an alternative explanation may be that lower blood pressure in older persons with a lower function ability might compromise cerebral perfusion, as a result of a failing vascular system and thereby increase the risk of symptoms of apathy.

This study has several strengths. We used validated measures to assess the symptoms of apathy and depression. We clearly demonstrated that the relationship for lower blood pressure and symptoms of apathy was not confounded by symptoms of depression, as a sensitivity analysis among those without depressive symptoms showed similar results. However, there are limitations to be considered when interpreting our results. First, as a major limitation, we cannot make any causal inference as this study has a cross-sectional observational design. Second, because no neuroimaging data were available, we were unable to ascertain that lower functional ability indeed coincided with lower cerebral perfusion. Third, we analyzed a population using antihypertensive treatment and without a history of stroke, TIA or recent MI, which limits the extrapolation of our findings to the general population of the older old. Finally, we only used the GARS to estimate functional ability. Although there is no single criterion or definition for functional ability, the GARS score may not fully reflect functional ability in daily life.

Given the mentioned limitations, our results should be interpreted with caution. Our findings contribute to increasing observational evidence that in older persons with lower functional ability, a lower blood pressure is associated with adverse health outcomes[13]. Therefore, future studies should determine if older persons with lower functional ability could benefit from less stringent blood pressure targets to prevent symptoms of apathy and other adverse health outcomes. If so, lower functional ability may become an important criterion for treatment decisions regarding antihypertensive medication.

In conclusion, functional ability moderates the association for blood pressure and symptoms of apathy. In older persons with lower functional ability, those with a lower blood pressure had more symptoms of apathy.

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Chapter 5

Lower blood pressure, small vessel disease, and apathy in older persons with mild cognitive deficits

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Abstract

Background: In older persons, both high and low blood pressure (BP) are associated with symptoms of apathy. Population characteristics, such as burden of cerebral small vessel disease (CSVD), may underlie these apparently contradictory findings. We aimed to explore in older persons, whether the burden of CSVD affects the association between BP and apathy.

Design: cross-sectional study.

Setting: primary care setting, the Netherlands.

Participants: community-dwelling older persons (mean age 80.7 years, SD 4.1) with mild cognitive deficits and using antihypertensive treatment, participating in the baseline measurement of the MRI sub-study (n=210) of the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) Study Leiden.

Measurements: During home visits, BP was measured in a standardized way and apathy was assessed with the Apathy Scale (range 0-42). Stratified linear regression analyses were performed according to the burden of CSVD. A higher burden of CSVD was defined as ≥2 points on a compound CSVD score (range 0-3) defined as presence of white matter hyperintensities (>median), any lacunar infarct, and/or ≥2 microbleeds.

Results: In the entire population, those with a lower systolic and those with a lower diastolic BP had more symptoms of apathy (β=-0.35, p=0.01 and β=-0.66, p=0.02, respectively). In older persons with a higher burden of CSVD (n=50, 24%), both lower systolic BP (β=-0.64, p=0.02) and lower diastolic BP (β=-1.6, p=0.01) were associated with more symptoms of apathy, whereas no significant association was found between BP and symptoms of apathy in older persons with a lower burden of CSVD (n=160).

Conclusions: Particularly in older persons with a higher burden of CSVD, lower BP was associated with more symptoms of apathy. Adequate BP levels for optimal psychological functioning may vary across older populations with a different burden of CSVD.

Introduction

Apathy is defined as a lack of motivation and loss of interest in almost all daily activities and other persons, and is associated with a very high caregiver burden[1]. Apathy can occur as part of a depressive disorder[2] and is particularly prevalent in patients with neurodegenerative diseases; however, apathy also frequently occurs in the older general population[3].

Both cerebrovascular and cardiovascular disease are risk factors for apathy[4, 5]. In a longitudinal study among people with the age of 85 and above, cardiovascular pathology at baseline was associated with more symptoms of apathy during follow-up[6]. Results from other longitudinal studies suggest a bidirectional relation, demonstrating an association between apathy at baseline and incident vascular disease[7]. Although vascular disease in old age is a multifactorial result of accumulating damage, current blood pressure (BP) is a vascular factor that can still be treated. Cross-sectional studies show that both higher[8] and lower BP[9] are related to more symptoms of apathy.

High BP, especially in middle age, can lead to cerebrovascular damage[10] which, in turn, can lead to apathy[4, 5]. On the other hand, lower BP might lead to apathy via reduced cerebral blood flow[11] and older persons may vary in their ability to maintain cerebral blood flow in the presence of low BP[12]. Also, in older persons, population characteristics that affect the regulation of BP may influence its association with neuropsychiatric symptoms.

In the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) Study Leiden, we previously found that the cross-sectional association between lower BP and apathy was present only in those with worse functional ability; and we hypothesized that worse functional ability might be a proxy for a higher burden of cerebral small vessel disease (CSVD)[9].

In a sub-population of participants of the DANTE Study Leiden that also underwent magnetic resonance imaging (MRI), the present study investigated whether the relationship between BP and apathy differed depending on the burden of CSVD. Our hypothesis was that, in older persons with a higher burden of CSVD, a lower rather than a higher BP would be associated with more symptoms of apathy.

Methods

Study design and participants

Baseline data from the DANTE Study Leiden were used for this study. The DANTE Study Leiden, a randomized clinical trial, aimed to investigate whether in older persons with mild cognitive deficits, neuropsychological functioning would improve after temporary discontinuation of antihypertensive treatment. Details on the design of the study are described elsewhere[13]. In brief, from 2011-2013, 430 participants were included from general practices. Participants were included when they had mild cognitive deficits (defined as a Mini Mental State Examination [MMSE] score of 21-27) and used antihypertensive medication. Participants were excluded when they had a history of stroke, major cardiovascular disease including heart failure, a clinical diagnosis of dementia, or a systolic BP >160 mmHg. In a subset of the population (n=220), at baseline 3Tesla MRI scanning of the brain was performed. Participants were excluded from this sub-study if they had a contra-indication for MRI or were unwilling to participate in the MRI sub-study. Due to movement artefacts one participant was excluded, and nine other patients had missing data (on the outcome measure, or on MRI parameters), leaving 210 participants for the present analysis.
All patients gave informed consent to participate in the DANTE Study Leiden, which was approved by the Medical Ethics committee of the Leiden University Medical Center.

Measurement of BP

Using a digital sphygmomanometer (Omron M6 Comfort) BP was measured twice on the right arm in seated position; the average of the two measurements was used for the analyses. Pulse pressure (PP) was calculated as 'systolic BP minus diastolic BP' and mean arterial pressure (MAP) as '(2/3)·diastolic BP+(1/3)·systolic BP'.

Measurement of symptoms of apathy

Symptoms of apathy were measured with the Starkstein Apathy Scale[14]. This instrument uses self-report combined with clinical assessment to evaluate the presence of symptoms of apathy. It contains 14 items, each scored 0-3, yielding a total score of 0-42 with higher scores indicating more symptoms of apathy. A cut-off of ≥14 was used for clinically relevant apathy[14].

Brain imaging

Whole-brain, 3DT1-weighted (repetition time[TR]/echo time[TE]=9.7/4.6, flip angle[FA]=8°, voxel size=1.17x1.17x1.40mm) images were acquired on a 3 Tesla MRI scanner (Philips Medical Systems, Best, the Netherlands). Details on imaging

acquisition and image processing are described elsewhere[15]. For the evaluation of features of CSVD, fluid attenuated inversion recovery (FLAIR) (TR/TE=11 000/125 msec, FA=90°), T2*-weighted (TR/TE=45/31 msec, FA=13°) and T2-weighted images (TR/TE=4200/80msec, FA=90°) were used. White matter hyperintensity (WMH) volume was quantified on FLAIR MRI in a semi-automated manner using the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Version 5.0.1. Library (FSL; www.fmrib.ox.ac.uk/fsl)[15, 16]. A trained single rater (JFD), blinded for clinical data, visually scored cerebral microbleeds and lacunar infarcts. A second rater (JG) with more than 15 years of neuroradiological experience supervised the rating. Lacunar infarcts were assessed on FLAIR and T2- and 3DT1-weighted images. Parenchymal defects (signal intensity identical to cerebrospinal fluid on all sequences) of ≥3 mm in diameter, surrounded by a zone of parenchyma with increased signal intensity on T2-weighted and FLAIR images, were defined as lacunar infarcts. Cerebral microbleeds were defined as punctate hypointense foci (on T2 images), which increased in size on T2*-weighted images (blooming effect)[17]. Symmetric hypointensities in the basal ganglia, likely to represent calcifications or non-hemorrhagic iron deposits, were disregarded.

Measurement of burden of CSVD

As of yet, no universal scale for burden of CSVD is available. Based on previous literature and available MRI features, the burden of CSVD was defined as having ≥2 of the following features: high WMH volume (dichotomized based on the median volume), presence of any lacunar infarct, and/or the presence of ≥2 microbleeds[18-20]. The role of cortical atrophy was assessed separately.

Other measurements

Sociodemographic factors were assessed using a structured clinical interview. Information on medication and medical history was obtained from the general practitioner's records. Level of education was dichotomized at 6 years of education. Use of alcohol was dichotomized at 14 units per week. The presence of a chronic disease was defined as ≥1 of the following: diabetes mellitus, Parkinson's disease, osteoarthritis, or a malignancy. Presence of cardiovascular disease was defined as ≥1 of the following: peripheral vascular disease, myocardial infarction >3 years ago, or a coronary reperfusion intervention >3 years ago (comprising percutaneous cardiac intervention and/or coronary artery bypass graft). Participants with a recent (<3 years ago) history of myocardial infarction or recent (<3 years ago) coronary reperfusion were excluded from the DANTE Study for safety reasons. Use of psychotropic medication was defined as using ≥1 of the following: antidepressants, antipsychotics, or benzodiazepines.

Depressive symptoms were measured with the Geriatric Depression Scale-15 (GDS-15)[21]. Since three items of the GDS-15 have a strong overlap with symptoms of apathy[6, 22],

only the remaining 12 items (GDS-12) were used in this analysis (range 0-12; higher scores indicating more symptoms). Functional ability was measured with the Groningen Activity Rating Scale (GARS)[23] (range 18-72; higher scores indicating worse functional ability). Global cognitive function was measured with the MMSE[24] (range 0-30; higher scores indicating better cognitive function). A high amount of global cortical atrophy was defined as low grey matter volume[25], dichotomized on the median.

Statistical analysis

Data are presented as mean with standard deviation (SD), median with interquartile range (IQR), or number with percentage, where appropriate. The association between BP and symptoms of apathy was tested using linear regression. Betas (β) with 95% confidence intervals (CI) and p-values were calculated per 10 mmHg increase in BP as the independent variable and continuous Apathy Scale scores as the outcome variable. Based on previous knowledge of potentially important confounders, all analyses were adjusted for age, sex, level of education, use of alcohol, and the use of psychotropic medication.

Stratified analyses were performed to investigate whether the association between BP and symptoms of apathy differed between older persons with a higher/lower burden of CSVD. The groups were split based on the cut-off of ≥2 features of CSVD[19]. To investigate the presence of statistical interaction, interaction terms (continuous BP parameter x burden of CSVD) were added to the linear regression models and p-values were calculated. To investigate the role of global neocortical atrophy in the association between BP and apathy, we separately stratified for the amount of global cortical atrophy. Furthermore, global cortical atrophy was added to the CSVD compound score, and the stratified analysis for higher/lower burden of CSVD was repeated using a cut-off of ≥2 features. Because the role of microbleeds might differ based on their localization[17], separate analyses were performed for lobar/non-lobar microbleeds. Unless stated otherwise, p-values for the continuous associations are presented. A p-value of <0.05 was considered statistically significant.

Results

Sociodemographic and clinical characteristics

Table 5.1 presents details on the population of the DANTE Study Leiden MRI sub-study; mean age was 80.7 (4.1) years, and 57.1% was female. Clinically relevant apathy was present in 22.9% of the population and, at baseline, all participants used antihypertensive treatment.

Table 5.1 Characteristics of participants of the DANTE MRI sub-study (n=210)

Demographic	
Age (years)	80.7 (4.1)
Female	120 (57.1)
> 6 years of education	150 (71.4)
Clinical	
Current smoking	16 (7.6)
Use of alcohol[a]	21 (10.0)
History of CVD[b]	17 (8.1)
Presence of chronic disease[c]	131 (61.9)
Use of psychotropic medication[d]	35 (16.7)
Use of beta blockers	78 (37.1)
Psychological and physical functioning	
Apathy Scale score[e]	10.7 (4.5)
Apathy Scale ≥14	48 (22.9)
GDS-12 score[f]	1 (0-2)
MMSE score[g]	26 (25-27)
GARS score[h]	22 (19-28)
Blood pressure parameters (mmHg)	
Systolic blood pressure	145.6 (21.1)
Diastolic blood pressure	80.6 (10.7)
Pulse pressure	65.0 (15.4)
Mean arterial pressure	102.3 (13.2)
Features of cerebral small vessel disease	
White matter hyperintensity volume (mL)	20.9 (8.8-56.2)
High white matter hyperintensity volume[i]	103 (49.0)
Any lacunar infarct present	57 (27.1)
≥2 microbleeds present	28 (13.3)
High burden[j]	51 (23.8)

Data are presented as mean (SD), number (%), or median (IQR) when appropriate

a: dichotomized at ≥14 units per week

b: CVD, cardiovascular disease: myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft ≥3 years before, peripheral arterial disease

c: chronic diseases comprise ≥1 of type 2 diabetes, Parkinson's disease, chronic obstructive pulmonary disease, osteoarthritis, and/or malignancy

d: psychotropic medication comprises ≥1 of antipsychotic and antidepressant medication, benzodiazepines

e: Apathy Scale. Range 0-42, higher scores indicate more symptoms of apathy

f: Geriatric Depression Scale-12. Range 0-12, higher scores indicate more symptoms of depression

g: MMSE, Mini Mental State Examination. Range 0 -30, higher scores indicate better cognitive function

h: GARS, Groningen Activity Rating Scale. Range 18-72 points, higher scores indicate worse functional status

i: dichotomized at the median

j: Higher burden of CSVD, cerebral small vessel disease, is defined as presence of ≥2 out of high white matter hyperintensity volume, any lacunar infarct, ≥2 microbleeds

Association between BP and apathy

In the entire population (n=210), those with a lower systolic and those with a lower diastolic BP had more symptoms of apathy (β=-0.35, p=0.01 and β=-0.66, p=0.02, respectively). A lower MAP was also associated with more symptoms of apathy (β=-0.59, p=0.01) while PP was not significantly associated with symptoms of apathy (β=-0.37, p=0.07). None of the BP parameters was associated with symptoms of depression (data not shown).

Association between BP and apathy in strata of CSVD

Table 5.2 shows the association between BP parameters and symptoms of apathy in the strata of higher/lower burden of CSVD. In those with a higher burden of CSVD, lower systolic BP (β=-0.64, p=0.02), lower diastolic BP (β=-1.6, p=0.01), and lower mean arterial pressure (β=-1.1, p=0.01) were associated with more symptoms of apathy. In contrast, there was no significant association between any of the BP parameters and symptoms of apathy in those with a lower burden of CSVD. The p-value for interaction was 0.29 for systolic BP and 0.04 for diastolic BP. No BP parameters were associated with symptoms of depression in any of the groups (data not shown).

Figure 5.1 shows a consistent pattern of a stronger association of lower BP and symptoms of apathy in the presence of CSVD, when stratifying on the separate CSVD features.

When stratified for global cortical atrophy, a lower systolic BP was associated with more symptoms of apathy in those with more global cortical atrophy (β= -0.54, p=0.02), whereas this association was absent in those with less global cortical atrophy (β=-0.15, p=0.38). Diastolic BP was not associated with symptoms of apathy in either stratum of global cortical atrophy (β=-0.79, p=0.09 in those with more global cortical atrophy, and β=-0.23, p=0.50 in those with less global cortical atrophy). When global cortical atrophy was added to the CSVD compound score, the results did not change. The results did not differ between older persons with lobar or non-lobar microbleeds. Additional adjustment for cognitive function (MMSE) or presence of chronic diseases did not change the results (data not shown).

Table 5.2 Mean scores of Apathy Scale per blood pressure level, stratified by cerebral small vessel disease (n=210)

Higher burden of cerebral small vessel disease (n=50)				Lower burden of cerebral small vessel disease (n=160)				
	Mean (SE)	**β (95% CI)**	***P***		**Mean (SE)**	**β (95% CI)**	***P***	***P* for interaction**
Systolic blood pressure				**Systolic blood pressure**				
Low (n=14)	12.8 (1.2)			Low (n=58)	11.0 (0.57)			
Middle (n=15)	11.3 (1.2)			Middle (n=54)	10.4 (0.58)			
High (n=21)	11.3 (0.96)			High (n=48)	9.7 (0.63)			
Per 10 mmHg		-0.64 (-1.12 to -0.12)	*0.02*	*Per 10 mmHg*		-0.24 (-0.57 to 0.09)	0.15	0.29
Diastolic blood pressure				**Diastolic blood pressure**				
Low (n=16)	14.4 (1.0)			Low (n=53)	11.0 (0.60)			
Middle (n=17)	10.5 (1.0)			Middle (n=53)	10.8 (0.59)			
High (n=17)	10.3 (0.98)			High (n=54)	9.4 (0.59)			
Per 10 mmHg		-1.6 (-2.8 to -0.46)	*0.01*	*Per 10 mmHg*		-0.38 (-1.0 to 0.25)	0.23	*0.04*
Pulse pressure				**Pulse pressure**				
Low (n=14)	12.8 (1.2)			Low (n=56)	10.9 (0.57)			
Middle (n=14)	11.3 (1.2)			Middle (n=54)	10.6 (0.59)			
High (n=22)	11.3 (0.95)			High (n=50)	9.6 (0.62)			
Per 10 mmHg		-0.71 (-1.5 to 0.08)	0.08	*Per 10 mmHg*		-0.27 (-0.72 to 0.19)	0.25	0.60
Mean arterial pressure				**Mean arterial pressure**				
Low (n=16)	13.7 (1.1)			Low (n=54)	11.1 (0.58)			
Middle (n=15)	10.5 (1.1)			Middle (n=54)	10.4 (0.58)			
High (n=19)	10.9 (0.97)			High (n=52)	9.6 (0.60)			
Per 10 mmHg		-1.1 (-2.0 to -0.32)	*0.01*	*Per 10 mmHg*		-0.38 (-0.90 to 0.14)	0.15	0.12

Unstandardized betas (β) with 95% confidence intervals (CI) calculated for each 10 mmHg increase in blood pressure. P for interaction between blood pressure parameter and burden of cerebral small vessel disease. All analyses adjusted for age, sex, level of education, use of alcohol, and use of psychotropic medication. Higher cerebral small vessel disease burden is defined as presence of ≥2 out of high white matter hyperintensity volume (dichotomized on the median), any lacunar infarct, ≥2 microbleeds

Tertiles of systolic blood pressure: low ≤136.5, middle 136.5-152, high >152 mmHg. Tertiles of diastolic blood pressure: low ≤76.0, middle 76.5-84.5, high ≥85 mmHg. Tertiles of pulse pressure: low ≤58.0, middle 58.5-69.0, ≥69.5 mmHg. Tertiles of mean arterial pressure: low ≤97.0, middle 97.2-107.0, high ≥107.5 mmHg.

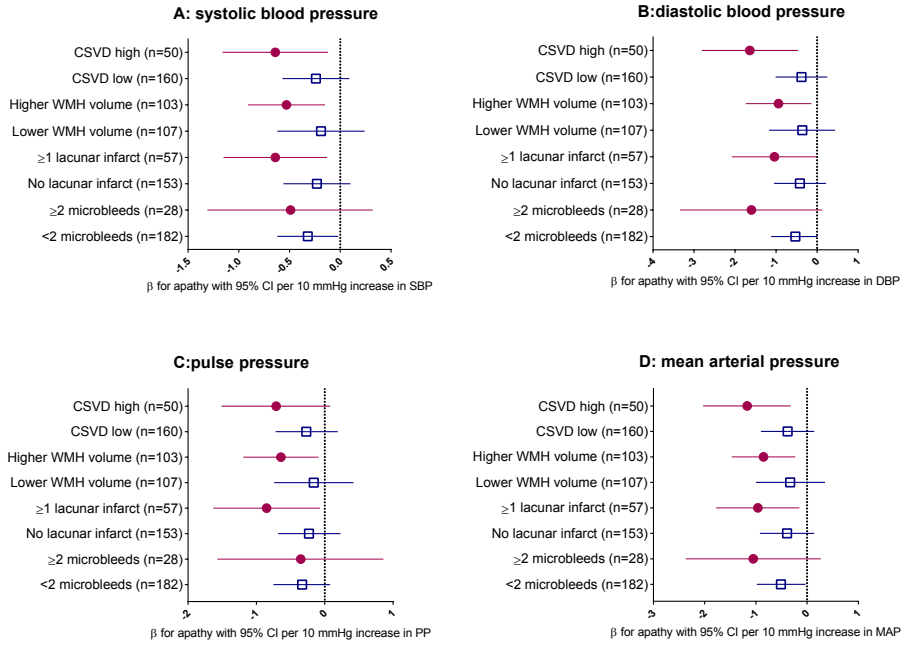

Figure 5.1 Association between blood pressure parameters and symptoms of apathy in strata of different features of cerebral small vessel disease

CSVD denotes cerebral small vessel disease; WMH, white matter hyperintensity; β, beta; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure. All analyses adjusted for age, sex, level of education, use of alcohol, and use of psychotropic medication. Higher cerebral small vessel disease (CSVD) burden is defined as presence of ≥2 out of: high white matter hyperintensity volume (dichotomized on the median), any lacunar infarct, ≥2 microbleeds.

Discussion

This study among community-dwelling older persons with mild cognitive deficits using antihypertensive medication found that, in those with a higher burden of CSVD, lower BP was associated with more symptoms of apathy. In contrast, in older persons with a lower burden of CSVD, BP was not associated with symptoms with apathy.

Although there is extensive evidence for the association between BP and cognitive function[12], few studies have investigated the association between BP and symptoms of apathy. The present findings extend our previous results showing that lower BP is cross-sectionally associated with symptoms of apathy only in those with worse functional ability measured with the Groningen Activity Restriction Scale[9]. In contrast to our findings, the Netherlands Study of Depression in Older persons (NESDO)

demonstrated that not a lower but a higher BP was cross-sectionally associated with more symptoms of apathy in depressed older persons[8]. A possible explanation for this discrepancy might be that the NESDO study population was substantially younger than the DANTE population and that in NESDO, cerebrovascular damage was not taken into account as a potential effect modifier. However, the NESDO Study found no association between BP and depression severity[8], which was confirmed in the present study. This supports the notion that apathy and depression in old age have specific risk factors and might be viewed as distinct clinical entities. Our findings of heterogeneity in the association between blood pressure and apathy are in line with studies showing that lower BP is specifically associated with worse cognitive function in older persons with worse functional ability[26], higher biological age[27], and a history of hypertension[28]. The relation between apathy and cognitive impairment may be bidirectional[29], since severity of cognitive impairment has been related to more symptoms of apathy[3], while apathy has also been shown to predict worse cognitive function[29]. In our study, adjusting our main analyses for cognitive function (MMSE) did not change the results, suggesting that cognitive function does not influence the association between apathy and BP in strata of CSVD.

Although no causal relations can be inferred from the present study due to the cross-sectional design, we can speculate on potential mechanisms underlying the association between lower BP and apathy in those with a higher burden of CSVD. First, older persons with a higher burden of CSVD may be unable to maintain their cerebral perfusion in the presence of low systemic BP. This hypothesis is supported by the finding of impaired cerebral blood flow in persons with more CSVD[30]. If impaired cerebral blood flow occurs in regions involved in the regulation of drive and motivation[31], this might explain why we found an association between lower BP and symptoms of apathy in those with more CSVD. This is further supported by the finding that lower BP was also associated with symptoms of apathy in those older persons with more global cortical brain atrophy, which has also been associated with worse cerebral perfusion[32, 33]. However, the DANTE trial demonstrated that a 4-month elevation of BP does not lead to a reduction in symptoms of apathy[13]. An alternative explanation might be that cardiac dysfunction is related to both lower BP and apathy. Although older people with a diagnosis of heart failure were excluded from the DANTE Study Leiden because of safety issues, even sub-clinical heart failure is linked to a lower BP[34] and might also be associated with more neuropsychiatric symptoms, including apathy[35].

This study has several strengths. First, the DANTE population is a well-defined population of community-dwelling older persons. Apathy was measured with an instrument specifically designed to measure symptoms of apathy and the inter-rater variability of this instrument in the DANTE Study Leiden was low[13]. Also, being the main determinant in the DANTE Study, BP was measured very carefully.

However, several limitations also need to be considered. First, the cross-sectional design not only hampers causal inference, but also does not rule out the possibility of reversed causality. In this respect, a recent meta-analysis of longitudinal studies demonstrated that apathy is an independent risk factor for cardiovascular disease[7]. Second, although we adjusted for potential confounders, the possibility of residual confounding cannot be ruled out. Further, some of the subgroups consisted of relatively low numbers. However, our findings are consistent among multiple sub groups (e.g. those with high total CSVD load, high WMH volume, and presence of lacunar infarcts) and across the different BP measures. Also, no measurements of (sub-clinical) heart failure were available in the DANTE Study Leiden, because no blood samples were taken and no echocardiograms/electronic cardiograms were performed. Lastly, the DANTE population was selected to participate in a clinical trial. This inevitably led to a selection of relatively well-functioning older persons and, probably, those with the highest levels of apathy were less likely to participate; this limits the generalizability of our results.

Although these limitations preclude our findings from being directly translated into clinical practice, the study does generate new hypotheses for further research. For example, in studies that also measure cardiac function[36], the hypothesis can be tested that the relation between lower BP and apathy is at least partly explained by sub-optimal cardiac function in older persons with CSVD. Furthermore, future trials investigating the effect of lowering of BP or, conversely, the effect of discontinuation of antihypertensive treatment, should take into account that the beneficial effects on apathy may vary between sub-populations of older persons.

In conclusion, in this study among older persons with mild cognitive deficits using antihypertensive medication, particularly in those with a higher burden of CSVD, lower BP was associated with more symptoms of apathy. Adequate BP levels for optimal psychological functioning may vary across older populations with a different burden of CSVD.

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Chapter 6

Blood pressure, cerebral small vessel disease, and neurocognitive functioning: The AGES-Reykjavik Study

Manuscript in preparation. Bertens AS, Haight TJ, Meirelles O, Sigursson S, Gudnason V, van Buchem MA, Muller M, Launer LJ. Blood pressure, cerebral small vessel disease, and neurocognitive functioning: The AGES-Reykjavik Study.

Abstract

Background: Hemodynamic disturbances, such as those reflected in low late-life blood pressure (BP), may lead to worse neurocognitive functioning, particularly in the presence of cerebral small vessel disease (CSVD), which may disturb cerebral autoregulation. We therefore hypothesized that in persons with CSVD, lower BP will lead to worse neurocognitive functioning.

Methods: We conducted a cross-sectional study based on 4,014 non-demented older individuals (mean age 76±5 years) who participated in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. Apathy was measured with the three apathy items of the Geriatric Depression Scale (GDS)-15, the GDS-3A (scores of ≥2 compared to<2), depressive symptoms with the remaining GDS-12D items (scores of ≥2 compared to<2), and cognition with domain-specific compound scores. Features of CSVD comprised 1) highest quartile of white matter lesion (WML) volume; 2) ≥1 subcortical infarct; 3) ≥1 microbleed; 4) ≥1Virchow-Robin space; 5) lowest quartile of total brain parenchymal volume. Multivariate logistic and linear regression models were used.

Results: In the entire study population, participants with lower systolic BP (SBP) (≤120 mmHg) were significantly more likely to have depressive symptoms compared to those with higher SBP (>140 mmHg) (odds ratio OR 1.46 (95% confidence interval 1.13-1.89), P-trend 0.002). This association was not affected by CSVD status. Only among the 884 participants with a higher burden of CSVD (≥2 features), participants with lower SBP had more symptoms of apathy than those with higher SBP (OR 3.55 (1.95-6.49), P-trend<0.001, P for interaction between SBP and CSVD<0.001)). There was no clear association between BP and cognitive function and this association was not affected by CSVD status.

Conclusions: In this study among community-dwelling older persons without dementia, lower SBP was related to more depressive symptoms in the entire study population. Only in those with a higher burden of CSVD, lower SBP was associated with more symptoms of apathy. Our study suggests that the burden of CVSD is critical for the relation between BP and apathy, but not for the relation between BP and depression or cognitive function.

Introduction

Cognitive decline in older age is often accompanied by other neuropsychiatric symptoms such as depression and apathy[1, 2], contributing to a larger burden of disease[3], more disability[4], and impaired quality of life[5]. Since apathy and depression can also occur as syndromes in the absence of cognitive impairment[6, 7], it is important to investigate risk factors for these different symptom profiles.

Cardiovascular disease and risk factors, and specifically blood pressure (BP), have been related to cognitive decline, symptoms of depression, and apathy in old age[8-10]. However, while evidence on the detrimental effects of hypertension in middle age is ample[11], both higher and lower late-life BP have been associated with worse cognitive function[12] and more neuropsychiatric symptoms[13-15].

Population characteristics may underlie these differences[16]. Indeed, previous studies found that lower BP was only related to worse cognitive function in older persons with mid-life hypertension[17] and worse functional status[18, 19], factors that are strongly related to vascular brain damage[17, 20]. It has been hypothesized that specifically in older persons with impaired cerebral regulatory mechanisms, such as in persons with cerebral small vessel disease(CSVD)[21, 22], hemodynamic disturbances such as lower BP might be related to neuropsychiatric symptoms[23, 24]. As of yet, the role of CSVD in the association between late-life blood pressure and symptoms of depression and apathy has not been described for the general older population. Moreover, no study on the effect of BP on the aging brain combined cognitive function, symptoms of depression, and apathy as outcome measures.

Therefore, in the Age Gene/Environment Susceptibility (AGES)-Reykjavik Study, a population-based study among older persons, we aimed to investigate whether the association between late-life BP and neurocognitive functioning, comprising the neuropsychiatric symptoms depression and apathy, and cognitive function, was different for those older persons with a higher and lower burden of CSVD. We hypothesized that in older persons with more CSVD, lower BP would be associated with worse neurocognitive functioning.

Methods

Participants

This study was performed with data from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, a population-based cohort study originating from the Reykjavik Study. A detailed description of the study design and initial assessments of the AGES-Reykjavik Study has been provided elsewhere[25]. In brief, in 2002, 5,764 randomly chosen surviving participants from the Reykjavik Study cohort were

examined for the AGES-Reykjavik Study. Examinations were completed within a 4- to 6-week time window.
The AGES-Reykjavik Study was approved by the National Bioethics Committee in Iceland (VSN 00-063) and by the National Institute on Aging Intramural Institutional Review Board. Written informed consent was obtained from all participants.

Measurement of apathy and depression

The Geriatric Depression Scale (GDS)-15[26] was administered to assess depressive symptoms. The GDS-15 has a range from 0-15, with higher scores indicating more depressive symptoms.
In factor analyses, three items of the GDS-15 have previously been identified as an instrument to measure symptoms of apathy[27, 28] including (1) "Have you dropped many of your activities and interests?" (2) "Do you prefer to stay at home, rather than going out and doing new things?", and (3) "Do you feel full of energy?". In line with previous reports in other population-based studies in older persons[15, 28] and the AGES-Reykjavik Study[29], these items were used as the "GDS-3A" to measure symptoms of apathy with a range of 0-3, and higher scores indicating more symptoms of apathy[30]. A cut-off score of ≥2 was used to indicate presence of apathy[30]. The remaining 12 items, the GDS-12D, were used as a subscale to measure symptoms of a depressed mood. A cut-off score of ≥2 was used to indicate presence of depressive symptoms[28, 31].

Measurement of cognitive function

Cognitive function was measured using an elaborate cognitive testing protocol comprising six different tests[32]. Three cognitive domain composite scores were calculated from these tests: (1) a memory composite score comprising the immediate and delayed recall of a modified version of the California Verbal Learning Test; (2) a processing speed composite score comprising the Figure Comparison Test, Digit Symbol Substitution Test, and Stroop 1 and 2; (3) an executive function composite score comprising a short version of the CANTAB Spatial Working Memory test, the Digits Backward test, and Stroop 3. Composite scores were computed by converting raw scores to standardized Z scores and averaging them across the tests in each composite score.

Measurement of blood pressure

Systolic BP (SBP) and diastolic BP (DBP) were averaged over two measurements in a seated position to the nearest 2 mmHg with a mercury sphygmomanometer. Based on the BP distribution of the population and clinical guidelines, SBP and DBP were divided into three categories[17]. For SBP, the categories were ≤120 mmHg, 121-140 mmHg, and >140 mmHg; for DBP the categories were ≤70 mmHg, 71-80 mmHg, and >80 mmHg.

Brain MRI measures

Magnetization resonance imaging (MRI) was performed on a 1.5T Signa Twinspeed EXCITE system (General Electric Medical Systems, Waukesha, WI). The image protocol was described in detail elsewhere[33] and included T1-, proton density-, T2*, and T2-weighted and fluid-attenuated inversion recovery (FLAIR) images.

As described previously[33, 34], brain volumes (in mL) were segmented automatically with an algorithm modified for the AGES-Reykjavik Study. Brain volumes comprised grey matter, white matter, WMLs, and cerebrospinal fluid (CSF). To calculate the intracranial volume (ICV), cerebrospinal fluid volume as well as grey matter, white matter, and WML volumes were summed up. Total brain parenchymal volume (the sum of grey matter, white matter, and WML volumes) was expressed as percent of ICV. Subcortical brain infarcts were identified by trained radiographers as defects with a diameter of at least 4mm in the brain parenchyma with associated hyperintensity on T2 and FLAIR. Cerebral microbleeds were defined as focal areas of signal void within the brain parenchyma that met the following criteria: visible on T2* images, smaller or invisible on T2 images, not abutting a parenchymal defect, and not showing any other structure in the signal void area[32].

Virchow-Robin spaces were defined as defects in the subcortical area without evidence of hemosiderin on the T_2*-weighted gradient-echo type echo planar scan and without a rim or area of high-signal intensity on fluid-attenuated inversion recovery. The presence of subcortical WMLs in frontal, occipital, parietal and temporal lobes were scored by trained radiographers using the Achten Scale. Hereby a semi-quantitative 'volumetric' estimation for WML load as provided, taking into account the lesion size and number[35]. WMLs were defined as visible hyperintense lesions on T2-weighted and FLAIR images.

Burden of cerebral small vessel disease

As described previously[36], features of CSVD were defined as 1) high WML volume (highest quartile vs rest), 2) ≥1 subcortical infarct; 3) ≥1 cerebral microbleed; 4) ≥1Virchow-Robin space; 5) low total brain parenchymal volume (lowest quartile vs rest). A composite score for burden of CSVD was computed by adding the points for each marker. The score was dichotomized into higher (≥2 points) or lower (0 or 1 point) burden of CSVD.

Other variables

A standardized questionnaire was filled out by the participants concerning medical history, medication use, and lifestyle factors[25]. Level of education was dichotomized at primary school level (low). The Mini-Mental State Examination[37] was used as a measure of global cognitive function. Smoking was defined as current or former vs never. Body mass index (BMI) was calculated based on weight and height (kg/m^2).

Fasting cholesterol and glucose levels were measured. A history of diabetes was defined as having a history of diabetes, using blood glucose-lowering medication, and/or a fasting glucose of ≥7.0mmol/l. A history of heart failure and history of stroke was based on self-report and hospital records. Presence of coronary heart disease (CHD) was defined as a self-reported history of coronary artery disease or coronary artery bypass surgery or angioplasty or angina on the Rose Angina Questionnaire (REF), or possible or probable myocardial infarction on electrocardiogram (ECG), or any CHD event (myocardial infarction, coronary artery bypass surgery, angioplasty, coronary heart disease) before entry into the AGES-Reykjavik study based on hospital records.
The number of comorbidities was assessed with a composite score of chronic kidney disease, liver disease, osteoarthritis, Parkinson's disease, any malignancy, and chronic obstructive pulmonary disease (COPD).

Analytical sample

Out of the 5,764 participants of baseline examination of the AGES-Reykjavik Study, 393 had a diagnosis of dementia and were excluded from these analyses because neurodegenerative diseases might influence BP regulation[38]. Of the remaining 5,371 participants, 4,949 had complete data on the GDS and BP measures. Additionally, 902 participants were excluded because of no MRI data or because of missing of the sequences necessary for brain segmentation, or there were artifacts in the scans that precluded processing. Reasons for not participating in the MRI study have been previously described[39]. A maximum of 0.7% of participants had missing data on covariates (n=30 on level of education, n=2 on BMI, n=2 on smoking status), leading to a total analytical sample of 4,014 participants.

Statistical analysis

Data are presented as number (n) with percentage (%), mean (±standard deviation, SD), or median (interquartile range, IQR). The cross-sectional associations between BP measurements and dichotomous GDS-3A and GDS-12D scores were assessed by logistic regression. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for each of the lower and middle BP categories, compared to the higher category as the reference group, using GDS-3A and GDS-12D scores as outcome variables. P-values for trend were calculated by using BP categories as continuous variables.
The cross-sectional associations between BP measurements and cognitive measures were assessed with linear regression models. P-values for trend over the BP categories were calculated with linear regression using BP categories as the determinant. Mean differences between cognitive scores in the different BP categories were calculated using the highest BP category as the reference group.

Associations were assessed in a minimally adjusted model (model 1, adjusted for age, gender, and level of education) and in a fully adjusted model (model 2, age, gender, level of education, BMI, total serum cholesterol, smoking status, history of diabetes, use of antihypertensive medication, history of heart failure, history of coronary artery disease, history of stroke, antidepressant therapy, and number of comorbidities). For depression and apathy, model 2 was also adjusted for MMSE score. For apathy and cognition, model 2 was also adjusted for GDS-12D scores. Unless stated otherwise, results for model 2 are shown.

To assess whether the association between BP and neurocognitive functioning was modified by the burden of CSVD, we performed stratified analyses in those participants with a lower and higher burden of CSVD. Next, we stratified the analyses on the individual features of CSVD. Because apathy has been previously shown to be related to white matter lesion load in the frontal lobe[29], we assessed whether the association between BP and symptoms of apathy was modified by white matter lesion load in the frontal, temporal, parietal and occipital lobes. For all of the potentially modifying CSVD features, statistical interaction was tested by adding an interaction term (feature of interest*BP categories) to the regression models.

Results

Baseline characteristics of the study population

Table 6.1 shows the characteristics of the study population. The mean age was 76 (5.3) years and 58% was female. Mean SBP was 142 (20) mmHg and 63% of the participants was using antihypertensive medication. Symptoms of depression were present in 18% of the participants and symptoms of apathy in 49%, respectively. A higher burden of CSVD was present in 22% of the participants.

Association between blood pressure and neurocognitive functioning in the entire study population

Table 6.2 shows that in the entire study population, those participants with SBP ≤120 mmHg had more depressive symptoms than those with SBP>140 mmHg (OR 1.46 (1.13-1.89), p Trend over BP categories 0.002). SBP was not associated with symptoms of apathy in the entire study population (Table 6.2). No clear association was found between SBP and memory, speed, and executive function (Table 6.3). DBP was not associated with symptoms of apathy and depression, nor with cognitive scores (supplementary Tables S6.1, S6.2).

Table 6.1 Characteristics of the study population (n=4,014)

Age (mean, SD)	76 (5.3)
Female gender (n, %)	2344 (58)
Low level of education (n, %)	903 (23)
Current use of alcohol (n, %)	2630 (66)
Current or former smoker (n, %)	2291 (57)
BMI (kg/m^2)	27 (4.3)
Total cholesterol (mmol/L)	5.6 (1.15)
History of diabetes (n, %)	541 (11)
Heart failure (n, %)	213 (5)
Coronary heart disease (n, %)	982 (25)
History of stroke (n, %)	309 (8)
Number of non-cardiovascular comorbidities (median, IQR)	1 (0-1)
SBP (mmHg)	142 (20)
DBP (mmHg)	74 (9.6)
Antihypertensive medication (n, %)	2521 (63)
GDS-3A score ≥2 (n, %)	1962 (49)
GDS-12D score ≥2 (n, %)	716 (18)
History of major depressive disorder (n, %)	192 (5)
Antidepressant medication (n, %)	539 (13)
MMSE (median, IQR)	27 (26-29)
ADL score	0 (0-1)
CSVD composite score ≥2	884 (22)
High WML volume[a] (n, %)	999 (25)
Any lacunar infarct (n, %)	444 (11)
Any microbleed (n, %)	448 (11)
Any perivascular space (n, %)	567 (14)
Low parenchymal volume[b] (n, %)	993 (25)

Abbreviations: BMI, body mass index; IQR: interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; GDS, geriatric depression scale (range 0-3 for GDS-3A and 0-12 for GDS-12D, higher scores indicate more symptoms); MMSE, mini mental state examination (range 0-30, higher scores indicate better cognitive function); ADL, activities of daily living (range 0-5, higher scores indicate worse performance); CSVD, cerebral small vessel disease; WML, white matter lesions

a: defined as the highest quartile of WML volume

b: defined as the lowest quartile of brain parenchymal volume

Table 6.2 Relation between systolic blood pressure and symptoms of apathy and depression (entire sample)

	GDS-3A ≥2, OR (95% CI)	GDS-12D ≥2, OR (95% CI)
Systolic blood pressure		
Model 1		
>140 (ref) (n=2,004)	1.00	1.00
121-140 (n=1,504)	1.09 (0.95-1.25)	1.15 (0.97-1.38)
≤120 (n=506)	1.16 (0.95-1.42)	***1.45 (1.14-1.86)***
p Trend	0.10	***0.003***
Model 2		
>140 (ref) (n=2,004)	1.00	1.00
121-140 (n=1,504)	1.13 (0.98-1.30)	1.19 (0.99-1.43)
≤120 (n=506)	1.13 (0.92-1.39)	***1.46 (1.13-1.89)***
p Trend	0.10	***0.002***
Model 2 + GDS-12D scores		
>140 (ref) (n=2,004)	1.00	-
121-140 (n=1,504)	1.09 (0.94-1.26)	-
≤120 (n=506)	1.04 (0.84-1.29)	-
p Trend	0.45	

Model 1: age, sex, level of education

Model 2: adjusted for age, sex, level of education, BMI, DM, cholesterol, smoking status, antihypertensive treatment, history of coronary artery disease, history of heart failure, history of stroke, antidepressant treatment, MMSE

Association between blood pressure and neurocognitive functioning in strata of cerebral small vessel disease

When we stratified the analyses based on a lower or higher burden of CSVD, an association between lower SBP and more symptoms of apathy was found only in those with a higher burden of CSVD, as shown in Table 6.4. No significant association between SBP and symptoms of apathy was found in those with a low burden of CSVD (P for interaction between burden of CSVD and SBP <0.001).

Table 6.3 Association between systolic blood pressure and cognitive function

	Memory		Processing speed		Executive function	
	Mean	**Mean difference**	**Mean**	**Mean difference**	**Mean**	**Mean difference**
Model 1						
>140 (ref)	0.10 (0.02)	Ref	0.12 (0.02)	Ref	0.06 (0.01)	Ref
121-140	0.14 (0.02)	-0.04 (-0.09 to 0.02)	0.13 (0.02)	-0.01 (-0.05 to 0.03)	0.08 (0.02)	-0.02 (-0.06 to 0.02)
≤120	0.13 (0.04)	-0.03 (-0.10-0.05)	0.09 (0.03)	0.03 (-0.03 to 0.10)	0.10 (0.03)	-0.03 (-0.09 to 0.03)
P trend	0.26	-	0.55	-	0.25	-
Model 2						
>140 (ref)	0.10 (0.02)	Ref	0.12 (0.01)	Ref	0.06 (0.01)	Ref
121-140	0.14 (0.02)	-0.04 (-0.10 to 0.01)	0.13 (0.02)	-0.01 (-0.05 to 0.03)	0.08 (0.02)	-0.02 (-0.06 to 0.02)
≤120	0.15 (0.04)	-0.05 (-0.13 to 0.03)	0.11 (0.03)	0.01 (-0.05 to 0.07)	0.10 (0.03)	-0.04 (-0.10 to 0.02)
P trend	0.09	-	0.96	-	0.14	-

Memory: compound z-score of immediate and delayed recall of California verbal learning test and Digit Span forward. Processing speed: compound z-score of Figure Comparison test, Digit Symbol Substitution Test, and Stroop 1 and 2. Executive function: compound z-score of short version of CANTAB spatial working memory test, Digit Span backward, and Stroop 3.

Data are presented as mean (standard error) and mean differences (95% confidence interval) as compared to the reference category. Adjusted means, mean differences, and P trend were calculated with ANCOVA.

Model 1: age, gender, level of education.

Model 2: age, gender, level of education, BMI, cholesterol, smoking status, diabetes mellitus, use of antihypertensive medication, history of heart failure, history of coronary heart disease, history of stroke, antidepressant therapy, number of comorbidities, and GDS-12D scores.

Table 6.4 Relation between systolic blood pressure and symptoms of apathy and depression according to low or high burden of CSVD

	Low burden of cerebral small vessel disease			High burden of cerebral small vessel disease	
	GDS-3A ≥2, OR (95% CI)	GDS-12D ≥2, OR (95% CI)		GDS-3A ≥2, OR (95% CI)	GDS-12D ≥2, OR (95% CI)
Systolic blood pressure			**Systolic blood pressure**		
Model 1			*Model 1*		
>140 (ref) (n=1523)	1.00	1.00	>140 (ref) (n=505)	1.00	1.00
121-140 (n=1208)	1.02 (0.87-1.19)	1.19 (0.96-1.46)	121-140 (n=315)	***1.41 (1.05-1.89)***	1.11 (0.79-1.56)
≤120 (n=431)	0.99 (0.80-1.24)	***1.40 (1.05-1.86)***	≤120 (n=83)	***3.32 (1.85-5.94)***	***1.89 (1.13-3.16)***
p Trend	0.96	***0.01***	p Trend	***<0.001***	***0.04***
Model 2			*Model 2*		
>140 (ref) (n=1394)	1.00	1.00	>140 (ref) (n=475)	1.00	1.00
121-140 (n=1063)	1.06 (0.91-1.25)	1.24 (0.996-1.53)	121-140 (n=287)	***1.44 (1.06-1.97)***	1.05 (0.74-1.50)
≤120 (n=381)	0.94 (0.74-1.18)[a]	***1.38 (1.03-1.96)***[b]	≤120 (n=76)	***3.55 (1.95-6.49)***[a]	***2.00 (1.16-3.43)***[b]
p Trend	0.88	***0.01***	p Trend	***<0.001***	***0.048***
Model 2 + GDS-12D			*Model 2 + GDS-12D*		
>140 (ref) (n=1387)	1.00	-	>140 (ref) (n=473)	1.00	-
121-140 (n=1059)	1.02 (0.86-1.20)	-	121-140 (n=285)	**1.44 (1.05-1.97)**	-
≤120 (n=311)	0.86 (0.66-1.09)[c]	-	≤120 (n=76)	**3.26 (1.76-6.05)**[c]	-
p Trend	0.35		p Trend	***<0.001***	

Data are presented as odds ratios with 95% confidence intervals in comparison with the reference category

Model 1: adjusted for age, sex, level of education

Model 2: adjusted for age, sex, level of education, BMI, DM, cholesterol, smoking status, antihypertensive treatment, history of coronary artery disease, history of heart failure, history of stroke, antidepressant treatment, MMSE

a: p for interaction <0.001

b: p for interaction =0.50

c: p for interaction <0.001

To investigate this further, we assessed the relation between SBP and symptoms of apathy according to the separate features of CSVD. Figure 6.1 shows that the relation between SBP and symptoms of apathy is specifically different for those with low and high WML volume, and for those without and with VRS (P for interaction <0.001 and 0.02, respectively).

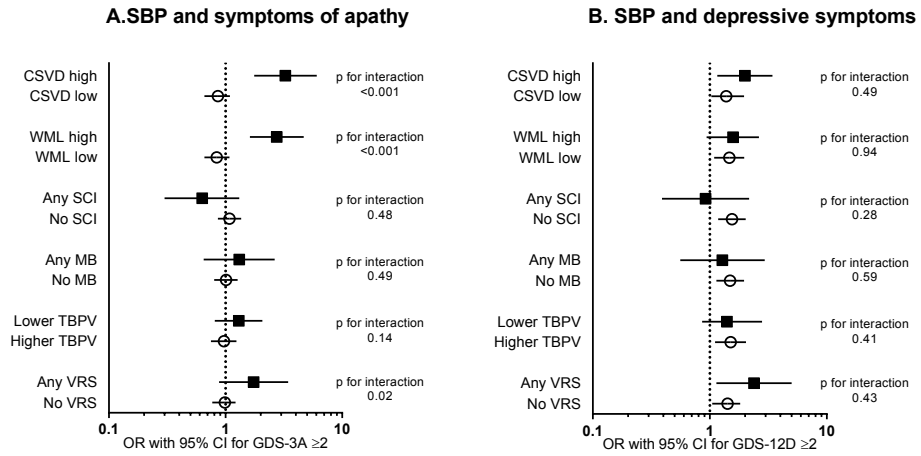

Figure 6.1 Relation between SBP and symptoms of apathy and depressive symptoms according to presence of features of cerebral small vessel disease

Odds ratios are caclulated for SBP<120 mmHg with SBP>140 mmHg as the reference category. CSVD denotes cerebral small vessel disease; WML, white matter lesions; SCI, subcortical infarcts; MB, microbleed; TPBV, total parenchymal brain volume; VRS, Virchow-Robin Space.

The association between SBP and symptoms of apathy was specifically different for those with a higher whole brain white matter lesion load (p for interaction 0.02), a higher frontal white matter lesion load (p for interaction 0.03) and a higher temporal white matter lesion load (p for interaction 0.01) (supplementary Figure S6.1). All directions of effects were that in those older persons with a higher lesion load, a lower SBP was associated with more symptoms of apathy.

Table 6.4 shows that lower SBP was related to more depressive symptoms in both strata of CSVD (p for interaction 0.50). No clear association was found between SBP and cognitive function, nor was this different for those with a higher or lower burden of CSVD (supplementary Table S6.4).

For DBP, no association with symptoms of apathy or depression was found in either stratum of CSVD (supplementary Table S6.3). Compared to those with a DBP of >90 mmHg, participants with DBP 71-80 mmHg and a higher burden of CSVD had a slower processing speed (mean difference 0.13 (0.01-0.24), supplementary Table S6.5).

Discussion

In this study among community-dwelling older persons without dementia, we found that lower SBP was related to more depressive symptoms in the entire study population. Furthermore, our study suggests that the presence and burden of CVSD is critical for the relation between BP and apathy, but not for the relation between BP and depression or cognitive function. In more detail, we found that lower SBP was associated with more symptoms of apathy but only in those older persons with a higher burden of CSVD. The association of lower SBP and symptoms of apathy was independent of depressive symptoms and cognitive function, and was most prominent in those with a higher burden of white matter lesions, specifically in the frontal and temporal lobes. No clear association was found between BP and cognitive function. The association between SBP and depressive symptoms and cognitive function was not different for those with a higher or lower burden of CSVD. DBP was not related to depressive symptoms, symptoms of apathy, nor cognitive function.

While the design of the study hampers causal inference, we can hypothesize on pathophysiological explanations for our findings. In line with the findings from previous studies[14,17], we hypothesized that lower BP would specifically be associated with worse neurocognitive functioning in those older persons with a higher burden of CSVD. One potential mechanism is that lower BP leads to worse neurocognitive functioning through cerebral hypoperfusion, which may particularly play a role in areas with more CSVD[40]. This hypothesis held true for symptoms of apathy, but not for depressive symptoms or cognitive function. Possibly, specifically in those older persons with a higher burden of CSVD, lower systemic BP may lead to cerebral hypoperfusion in brain areas critical for regulation of motivation[41]. This hypothesis is supported by our finding that the relation between lower BP and symptoms of apathy was present in older persons with a higher frontal and temporal white matter lesion load. Lesions in these brain regions are associated with apathy[42,43] which might render these individuals particularly vulnerable to the effects of lower BP and hypoperfusion. However, the association between lower systemic BP and reduced cerebral blood flow is still under debate[44], with studies showing an association between hypertension and lower cerebral blood flow[45] and others failing to show an association[46]. An alternative explanation might be that lower SBP in fact reflects sub-optimal cardiac function[47]. It has been demonstrated that depressive symptoms occur frequently in older persons with sub-optimal cardiac function, even in the absence of symptomatic heart failure[48]. While the literature on sub-optimal cardiac function and apathy is scarce, it might be postulated that sub-optimal cardiac function is more strongly related to depressive symptoms than of apathy because of their fluctuating nature and relation with functional disability in

patients with heart failure. Conversely, there is increasing evidence that structural vascular brain damage might be more strongly related to symptoms of apathy than of depression[8, 29]. This might explain why in our study a higher burden of CSVD was a prerequisite for the association between lower SBP and symptoms of apathy, but not for depressive symptoms.

Our findings suggest that BP has a different association pattern with depressive symptoms than with symptoms of apathy. Earlier studies on the association between BP and depression and apathy show similar conflicting results. Both higher[13, 49] and lower BP[50, 51] have been related to depressive symptoms and to symptoms of apathy[13, 14] in older persons. It has been postulated that population differences underlie these conflicting findings[16]. Such differences might include chronological or biological age[52], the level of frailty[23] or, as we hypothesized, levels of CSVD. Indeed, a cross sectional study among participants of the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) Study Leiden, showed that lower BP was related to apathy in older persons with worse functional ability, which might be a proxy for CSVD[14]. While we demonstrated an association between lower BP and more depressive symptoms, in the DANTE Study Leiden BP was not related to depressive symptoms measured with the GDS-15.

In contrast to our hypothesis, we found no clear association between BP and cognitive function in both the entire study sample and when stratifying for burden of CSVD. The fact that the association between SBP and depression, apathy, and cognition differed substantially in our study, adds to the notion that apathy can be regarded as a separate clinical syndrome which can also occur outside the scope of major depressive disorder or dementia[53, 54]. Although we addressed these outcomes separately in our current study, no specific measure for apathy was available. However, the finding that the association between BP and the items on the GDS-3A differed from that on the GDS-12D, and that this remained despite adjustment for cognition and GDS-12D scores, suggests that results might have been similar with an instrument specifically targeting apathy.

This study has several strengths. Because we separately addressed symptoms of apathy, depression and cognitive function as outcome measures, we had the opportunity to study the potentially different effects of BP on these outcome parameters. The AGES-Reykjavik Study is a well-designed, well-described population-based study with rigorously defined parameters that we used as determinants and outcome measures and we were able to take many potential confounders into account. However, several limitations have to be taken into account when interpreting the results of this study. First, because of the cross-sectional design, no causal mechanisms can be inferred, which hampers direct translation into clinical practice. Although we adjusted for several disease-related and demographic characteristics, there still might be residual confounding. Further, because of the

lack of a specific instrument measuring apathy, we used the GDS-3A as a substitute measure. This instrument has a high specificity but low sensitivity[28,30] and therefore is not suitable for estimating prevalence of apathy in a study population. When studying associations with the GDS-3A however, it can be assumed that in case of non-differential misclassification, a bias toward the null would occur[30]. Last, because no definitive measure for the burden of CSVD is available as of yet, we used the available MRI measures to create a composite score which has been used before in literature[55]. Different measures will be available in different studies, hampering direct comparison of results.

In conclusion, in this study among community-dwelling older persons we found that lower BP was associated with more depressive symptoms. However, the relation between lower BP and symptoms of apathy was only present in those older persons with a higher burden of CSVD. No such relation was found between low BP and cognitive functioning. In the heart-brain axis, apathy and depression are often overlooked but important neuropsychiatric symptoms that might have specific risk factors as targets for prevention and treatment. Future studies should aim to better define patients who may be at higher risk to develop neuropsychiatric complications of lower BP and should investigate whether less stringent BP targets than currently recommended will prevent further brain damage in these patients so that more tailored advice for BP control can be given.

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Supplementary material

Table S6.1 Relation between diastolic blood pressure and symptoms of apathy and depression (entire sample)

	GDS-3A ≥2, OR (95% CI)	GDS-12D ≥2, OR (95% CI)
Diastolic blood pressure		
Model 1		
>80 (ref) (n=900)	1.00	1.00
71-80 (n=1627)	0.90 (0.76-1.07)	0.88 (0.71-1.10)
≤70 (n=1508)	0.92 (0.78-1.09)	0.98 (0.78-1.22)
p Trend	0.41	0.98
Model 2		
>80 (ref) (n=813)	1.00	1.00
71-80 (n=1473)	0.91 (0.77-1.08)	0.91 (0.73-1.14)
≤70 (n=1390)	0.90 (0.75-1.07)	0.98 (0.78-1.23)
p Trend	0.26	0.99
Model 2+GDS-12D scores		
>80 (ref) (n=808)	1.00	-
71-80 (n=1466)	0.92 (0.77-1.10)	-
≤70 (n=1387)	0.89 (0.74-1.07)	-
p Trend	0.25	

Model 1: age, sex, level of education

Model 2: adjusted for age, sex, level of education, BMI, DM, cholesterol, smoking status, antihypertensive treatment, history of coronary artery disease, history of heart failure, history of stroke, antidepressant treatment, MMSE

Table S6.2 Association between diastolic blood pressure and cognitive function

	Memory		Processing speed		Executive function	
	Mean	**Mean difference**	**Mean**	**Mean difference**	**Mean**	**Mean difference**
Model 1						
>80 (ref)	0.11 (0.03)	Ref	0.12 (0.02)	Ref	0.08 (0.02)	Ref
71-80	0.13 (0.02)	-0.03 (-0.09 to 0.04)	0.13 (0.02)	-0.01 (-0.06 to 0.04)	0.09 (0.02)	-0.01 (0.06 to 0.04)
≤70	0.11 (0.02)	-0.001 (-0.07 to 0.07)	0.11 (0.02)	0.01 (-[0.04 to 0.07)	0.05 (0.02)	0.03 (-0.03 to 0.08)
P trend	0.90	-	0.58	-	0.26	-
Model 2						
>80 (ref)	0.11 (0.03)	Ref	0.12 (0.02)	Ref	0.08 (0.02)	Ref
71-80	0.13 (0.02)	-0.02 (-0.09 to 0.04)	0.13 (0.02)	-0.01 (-0.06 to 0.04)	0.08 (0.02)	-0.01 (-0.06 to 0.04)
≤70	0.11 (0.02)	-0.01 (-0.07 to 0.06)	0.11 (0.02)	0.01 (-0.05 to 0.06)	0.05 (0.02)	0.02 (-0.03 to 0.07)
P trend	0.97	-	0.76	-	0.35	-

Memory: compound z-score of immediate and delayed recall of California verbal learning test and Digit Span forward. Processing speed: compound z-score of Figure Comparison test, Digit Symbol Substitution Test, and Stroop 1 and 2. Executive function: compound z-score of short version of CANTAB spatial working memory test, Digit Span backward, and Stroop 3

Data are presented as mean (standard error) and mean differences (95% confidence interval) as compared to the reference category. Adjusted means, mean differences, and P trend were calculated with ANCOVA

Model 1: age, gender, level of education

Model 2: age, gender, level of education, BMI, cholesterol, smoking status, diabetes mellitus, use of antihypertensive medication, history of heart failure, history of coronary heart disease, history of stroke, antidepressant therapy, number of comorbidities, GDS-12D score

Table S6.3 Relation between diastolic blood pressure and symptoms of apathy and depression according to low or high burden of CSVD

	Low burden of cerebral small vessel disease			High burden of cerebral small vessel disease	
	GDS-3A ≥2	GDS-12D ≥2		GDS-3A ≥2	GDS-12D ≥2
Diastolic blood pressure			**Diastolic blood pressure**		
Model 1			*Model 1*		
>80 (ref) (n=684)	1.00	1.00	>80 (ref) (n=221)	1.00	1.00
71-80 (n=1278)	0.85 (0.70-1.02)	0.94 (0.63-1.41)	71-80 (n=360)	1.13 (0.80-1.60)	0.74 (0.50-1.10)
≤70 (n=1200)	0.90 (0.74-1.09)	0.99 (0.65-1.49)	≤70 (n=322)	1.06 (0.74-1.52)	0.91 (0.61-1.37)
p Trend	0.39	0.66	p Trend	0.81	0.89
Model 2			*Model 2*		
>80 (ref) (n=611)	1.00	1.00	>80 (ref) (n=202)	1.00	1.00
71-80 (n=1136)	0.85 (0.70-1.04)	1.00 (0.77-1.31)	71-80 (n=337)	1.13 (0.79-1.62)	0.69 0.46-1.05)
≤70 (n=1091)	0.88 (0.72-1.08)	1.07 (0.82-1.41)	≤70 (n=299)	1.01 (0.69-1.47)	0.80 (0.52-1.22)
p Trend	0.29	0.57	p Trend	0.98	0.38
Model 2 + GDS-12D			*Model 2 + GDS-12D*		
>80 (ref) (n=608)	1.00	-	>80 (ref) (n=200)	1.00	-
71-80 (n=1130)	0.84 (0.69-1.03)	-	71-80 (n=336)	1.24 (0.85-1.80)	-
≤70 (n=1089)	0.86 (0.70-1.06)[c]	-	≤70 (n=298)	1.06 (0.72-1.56)[c]	-
p Trend	0.23	-	p Trend	0.87	-

Data are presented as odds ratios with 95% confidence intervals in comparison with the reference category

Model 1: adjusted for age, sex, level of education

Model 2: adjusted for age, sex, level of education, BMI, DM, cholesterol, smoking status, antihypertensive treatment, history of coronary artery disease, history of heart failure, history of stroke, antidepressant treatment, MMSE

a: p for interaction = 0.89

b: p for interaction =0.31

c: p for interaction =0.75

Table S6.4 The relation between systolic blood pressure and cognitive domains in strata of burden of CSVD

	Low burden of CSVD (<2 features, n=3,162)						High burden of CSVD (features, n=903)					
	Memory		Processing speed		Executive function		Memory		Processing speed		Executive function	
	Mean	Mean difference	Mean	Mean difference	Mean	Mean difference	Mean	Mean difference	Mean	Mean difference	Mean	Mean difference
Model 1												
>140 (ref)	0.19 (0.02)	Ref	0.21 (0.02)	Ref	0.12 (0.02)	Ref	-0.19 (0.03)	Ref	-0.19 (0.03)	Ref	-0.14 (0.03)	Ref
121-140	0.25 (0.02)	***-0.06 (-0.1 to -0.002)***	0.23 (0.02)	-0.02 (-0.07 to 0.02)	0.15 (0.02)	-0.03 (-0.07 to 0.02)	-0.25 (0.04)	0.06 (-0.05 to 0.17)	-0.25 (0.04)	0.06 (-0.05 to 0.17)	-0.16 (0.04)	0.02 (-0.08 to 0.11)
≤120	0.22 (0.04)	-0.03 (-0.12 to 0.05)	0.17 (0.03)	0.04 (-0.02 to 0.11)	0.15 (0.03)	-0.03 (-0.19 to 0.03)	-0.22 (0.09)	0.03 (-0.15 to 0.21)	-0.21 (0.08)	0.02 (-0.16 to 0.20)	-0.15 (0.73)	0.002 (-0.15 to 0.16)
P trend	0.16	-	0.52	-	0.23	-	0.45	-	0.45	-	0.83	-
Model 2												
>140 (ref)	0.18 (0.02)	Ref	0.21 (0.02)	Ref	0.12 (0.02)	Ref	-0.19 (0.03)	Ref	-0.19 (0.03)	Ref	-0.14 (0.03)	Ref
121-140	0.25 (0.02)	***-0.07 (-0.13 to -0.01)***	0.23 (0.02)	-0.02 (-0.07 to 0.02)	0.14 (0.02)	-0.02 (-0.07 to 0.02)	-0.26 (0.04)	0.07 (-0.05 to -0.17)	-0.26 (0.04)	0.07 (-0.04 to 0.17)	-0.16 (0.04)	-0.02 (-0.07 to 0.11)
≤120	0.24 (0.04)	-0.06 (-0.15 to 0.03)	0.19 (0.03)	0.02 (-0.05 to 0.09)	0.16 (0.03)	-0.04 (-0.11 to 0.02)	-0.22 (-0.09)	0.03 (-0.16 to 0.21)	-0.22 (0.08)	0.03 (-0.14 to 0.21)	-0.15 (0.07)	0.01 (-0.15 to 0.17)
P trend	***0.047***	-	0.97	-	0.14	-	0.41	-	0.35	-	0.74	-

Memory: compound z-score of immediate and delayed recall of California verbal learning test and Digit Span forward. Processing speed: compound z-score of Figure Comparison test, Digit Symbol Substitution Test, and Stroop 1 and 2. Executive function: compound z-score of short version of CANTAB spatial working memory test, Digit Span backward, and Stroop 3

Data are presented as mean (standard error) and mean differences (95% confidence interval) as compared to the reference category. Adjusted means, mean differences, and P trend were calculated with ANCOVA

Model 1: age, gender, level of education

Model 2: age, gender, level of education, BMI, cholesterol, smoking status, diabetes mellitus, use of antihypertensive medication, history of heart failure, history of coronary heart disease, history of stroke, antidepressant therapy, number of comorbidities, and GDS-12D scores

P for interaction; memory: 0.14; processing speed: 0.43; executive function: 0.48

Table S6.5 The relation between diastolic blood pressure and cognitive domains in strata of burden of CSVD

	Low burden of CSVD (<2 features, n=3,162)						High burden of CSVD (features, n=903)					
	Memory		Processing speed		Executive function		Memory		Processing speed		Executive function	
	Mean	Mean difference	Mean	Mean difference	Mean	Mean difference	Mean	Mean difference	Mean	Mean difference	Mean	Mean difference
Model 1												
>80 (ref)	0.20 (0.03)	Ref	0.21 (0.02)	Ref	0.13 (0.02)	Ref	-0.20 (0.05)	Ref	-0.17 (0.05)	Ref	-0.11 (0.05)	Ref
71-80	0.23 (0.02)	-0.03 (-0.11 to 0.04)	0.24 (0.02)	-0.03 (-0.09 to 0.02)	0.16 (0.02)	-0.03 (-0.09 to 0.02)	-0.18 (0.04)	-0.02 (-0.15 to 0.11)	-0.26 (0.04)	0.09 (-0.04 to 0.22)	-0.17 (0.04)	0.06 (-0.05 to 0.17)
≤70	0.21 (0.02)	-0.02 (-0.10 to 0.06)	0.19 (0.02)	0.02 (-0.04 to 0.08)	0.11 (0.02)	0.02 (-0.04 to 0.08)	-0.27 (0.04)	-0.07 (-0.07 to 0.20)	-0.20 (0.04)	0.03 (-0.11 to 0.16)	-0.16 (0.04)	0.06 (-0.06 to 0.17)
P trend	0.74		0.34		0.27		0.27		0.81		0.38	
Model 2												
>80 (ref)	0.19 (0.03)	Ref	0.20 (0.02)	Ref	0.13 (0.02)	Ref	-0.19 (0.05)	Ref	-0.16 (0.05)	Ref	-0.10 (0.05)	Ref
71-80	0.23 (0.02)	-0.04 (-0.11 to 0.04)	0.24 (0.02)	-0.04 (-0.10 to 0.02)	0.16 (0.02)	-0.03 (-0.09 to 0.21)	-0.19 (0.04)	0.01 (-0.12 to 0.14)	-0.29 (0.04)	***0.13 (0.01 to 0.24)***	-0.18 (0.04)	0.08 (-0.03 to 0.19)
≤70	0.22 (0.02)	-0.03 (-0.10 to 0.05)	0.19 (0.02)	0.01 (-0.05 t00.07)	0.11 (0.02)	0.02 (-0.04 to 0.08)	-0.26 (0.04)	0.08 (-0.06 to 0.21)	-0.18 (0.04)	0.02 (-0.11 to 0.15)	-0.15 (0.04)	0.05 (-0.07 to 0.17)
P trend	0.57		0.45		0.35		0.24		0.90		0.46	

Memory: compound z-score of immediate and delayed recall of California verbal learning test and Digit Span forward. Processing speed: compound z-score of Figure Comparison test, Digit Symbol Substitution Test, and Stroop 1 and 2. Executive function: compound z-score of short version of CANTAB spatial working memory test, Digit Span backward, and Stroop 3

Data are presented as mean (standard error) and mean differences (95% confidence interval) as compared to the reference category. Adjusted means, mean differences, and P trend were calculated with ANCOVA.

Model 1: age, gender, level of education

Model 2: age, gender, level of education, BMI, cholesterol, smoking status, diabetes mellitus, use of antihypertensive medication, history of heart failure, history of coronary heart disease, history of stroke, antidepressant therapy, number of comorbidities, and GDS-12D scores

P for interaction; memory: 0.36; processing speed: 0.86; executive function; 0.86

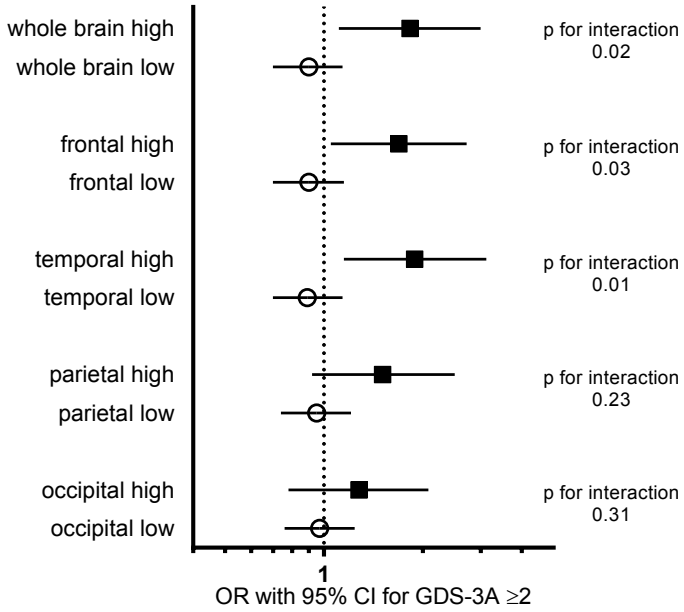

Figure S6.1 Relation between lower SBP and symptoms of apathy according to regional white matter lesion load

Odds ratios are caclulated for SBP<120 mmHg with SBP>140 mmHg as the reference category. OR denotes odds ratio; CI, confidence interval; GDS, Geriatric Depression Scale; SBP, systolic blood pressure

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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Chapter 8

Summary

Aim

The aim of this thesis was to investigate cardiovascular determinants of neurocognitive functioning in old age, in particular cognitive dysfunction, depressive symptoms, and apathy. First, we investigated whether the Geriatric Depression Scale (GDS)-3A, comprising the three apathy items of the GDS-15, can be used to measure symptoms of apathy in research settings. We further explored the role of cardiac function by investigating the relation between high sensitivity troponin T (hs-cTnT), a cardiac biomarker, and neurocognitive functioning in the Leiden 85-Plus Study. Next, by using data from the DANTE Study Leiden and the AGES-Reykjavik Study, we investigated how blood pressure was related to symptoms of apathy, depressive symptoms, and cognitive dysfunction. We tested the hypothesis that particularly in older persons with impaired capability to maintain optimal cerebral blood flow, such as individuals with poor functional ability and with a higher burden of cerebral small vessel disease (CSVD), lower rather than higher blood pressure would be related to worse neurocognitive functioning.

The validity of the GDS-3A to measure apathy in research settings

In **chapter 2,** we investigated the scale properties of the GDS-3A, a sub-set of the three 'apathy' questions of the frequently administered GDS-15, as compared to the Apathy Scale in both the DANTE Study Leiden and the PROMODE Study. In both studies, the GDS-3A only moderately discriminated between presence and absence of apathy; the sensitivity for apathy according to a cut-off of 2 or higher was low (29-33%), while specificity was high (89-93%). These findings suggest that, while not a useful instrument to screen for apathy in clinical practice, the GDS-3A can be used in research to study associations with risk factors. In case of non-differential misclassification, using the GDS-3A will yield estimates that are biased towards the null.

High sensitivity cardiac troponin T and neurocognitive functioning

In **chapter 3,** we studied the longitudinal association between the cardiac biomarker hs-cTnT and neurocognitive functioning in the oldest old, using data from the Leiden 85-Plus Study. During four years of follow-up, those older persons with the highest levels of hs-cTnT had a steeper annual decline in Mini Mental State Examination (MMSE) score. We demonstrated that this association is independent of sociodemographic

and cardiovascular risk factors. Moreover, the relation between higher levels of hs-cTnT and worse cognitive function was also found in those participants without a history of clinically overt cardiac disease, suggesting that hs-c-TnT may be a marker of microvascular coronary artery disease or global microvascular disease underlying processes of cognitive decline in older people. Levels of hs-cTnT were not related to more symptoms of apathy and inconsistently with symptoms of depression. Thus, hs-cTnT may be a more specific marker for cognitive dysfunction than for apathy and depression.

Blood pressure and neurocognitive functioning

In **chapter 4,** we used data from the DANTE Study Leiden to investigate the relation between blood pressure and symptoms of apathy measured with the Apathy Scale, and depressive symptoms measured with the GDS-15. We demonstrated that lower systolic and diastolic blood pressure were related to more symptoms of apathy in older persons with lower functional ability, while blood pressure measures were not related to apathy in older persons with higher functional ability. Blood pressure measures were not related to depressive symptoms in either stratum.
In **chapter 5** we used data from the DANTE Study Leiden MRI Sub Study to demonstrate that the association between a lower systolic and diastolic blood pressure and symptoms of apathy was present in those with a higher burden of CSVD, but not in those with a lower burden of CSVD. Blood pressure was not associated with depressive symptoms in the entire population, nor in either of the subgroups.
In **chapter 6**, we demonstrated that in the population-based AGES-Reykjavik Study, a lower systolic blood pressure was associated with more symptoms of depression measured with the GDS-12D. No clear association between blood pressure and cognitive measures was found. Blood pressure was not related to apathy as measured with the GDS-3A in the entire study sample. When we stratified for the presence of CSVD, lower blood pressure was related to symptoms of apathy only in those participants with a higher burden of CSVD. The associations between blood pressure on the one hand and depressive symptoms and cognitive function on the other hand, were not influenced by the burden of CSVD. Results from this study further add to the notion that cognitive dysfunction, symptoms of depression, and symptoms of apathy in older age may have different risk factor profiles.
In **chapter 7**, the main findings of this thesis are discussed. Our findings are placed in the light of the literature and we discuss methodological strengths and limitations. We propose hypotheses that might explain our findings and make recommendations for clinical practice and future studies.

In conclusion, we found that cardiovascular risk factors are important for neurocognitive functioning in older persons. Moreover, we found that specific cardiovascular determinants, such as blood pressure and hs-cTnT, have different associations with apathy than with depression and cognitive function.

Addendum

Nederlandse samenvatting

Vergeet het hart niet: cardiovasculaire determinanten van neurocognitief functioneren

Het doel van dit proefschrift was om de cardiovasculaire determinanten van neurocognitief functioneren op latere leeftijd te onderzoeken, met de nadruk op cognitieve achteruitgang, depressieve symptomen en apathie.

Ten eerste onderzochten we of de *Geriatric Depression Scale (GDS)-3A,* die bestaat uit de drie 'apathie'-vragen van de GDS-15, gebruikt kan worden om in wetenschappelijk onderzoek symptomen van apathie te meten. Tevens bestudeerden we de rol van hartfunctie door de relatie te onderzoeken tussen hogere waarden van *high sensitivity* troponine T (hs-cTnT), een cardiale *biomarker,* en neurocognitief functioneren in de Leiden 85-plus Studie. Vervolgens gebruikten we data van de DANTE Studie Leiden en de AGES-Reykjavik Studie om te onderzoeken hoe bloeddruk gerelateerd was aan symptomen van apathie, depressieve symptomen, en verminderd cognitief functioneren. We testten de hypothese dat vooral bij oudere mensen bij wie de regulatie van een optimale hersendoorbloeding verminderd is, zoals die met een gebrekkiger dagelijks functioneren en met meer cerebrale *small vessel disease* (CSVD), een lagere en niet een hogere bloeddruk gerelateerd is aan slechter neurocognitief functioneren.

De validiteit van de GDS-3A voor het meten van apathie in wetenschappelijk onderzoek

In **hoofdstuk 2** onderzochten we de schaaleigenschappen van de GDS-3A, de drie 'apathie' vragen van de veelgebruikte GDS-15, in vergelijking met de *Apathy Scale* in zowel de DANTE Studie Leiden als de PROMODE Studie. In beide studies onderscheidde de GDS-3A slechts in beperkte mate tussen de aan- en afwezigheid van apathie; de sensitiviteit voor apathie (met een afkappunt van twee of meer punten) was laag (29-33%), terwijl de specificiteit hoog was (89-93%). Hoewel de GDS-3A mogelijk geen nuttig instrument is om te screenen op apathie in de klinische praktijk, suggereren deze bevindingen dat de schaal wel gebruikt kan worden in wetenschappelijk onderzoek naar risicofactoren voor apathie. In het geval van non-differentiële misclassificatie zal het gebruik van de GDS-3A mogelijk leiden tot een onderschatting van het effect.

High sensitivity cardiale troponine T en neurocognitief functioneren

In **hoofdstuk 3** bestudeerden we de longitudinale associatie tussen de cardiale *biomarker* hs-cTnT en neurocognitief functioneren bij de oudste ouderen, waarbij we gebruik maakten van de data van de Leiden 85-plus Studie. Tijdens vier jaar *follow-up* gingen de deelnemers met de hoogste hs-cTnT-waarden jaarlijks sneller achteruit zoals vastgesteld met de *Mini Mental State Examination (MMSE).* We toonden aan dat deze associatie onafhankelijk is van sociodemografische en klinische risicofactoren. De relatie tussen hogere hs-cTnT-waardenen en snellere cognitieve achteruitgang werd bovendien ook gevonden bij deelnemers zonder een gediagnosticeerde hartziekte in de medische voorgeschiedenis, wat suggereert dat hs-cTnT wellicht een *marker* is van microvasculaire coronaire schade of van globale microvasculaire schade. Deze processen liggen mogelijk mede ten grondslag aan cognitieve achteruitgang bij oudere mensen. Hs-cTnT was niet gerelateerd aan symptomen van apathie en de relatie tussen hs-cTnT en depressieve symptomen was inconsistent. Hs-cTnT is wellicht meer een specifieke *marker* voor cognitieve achteruitgang dan voor apathie en depressie.

Bloeddruk en neurocognitief functioneren

In **hoofdstuk 4** gebruikten we data van de DANTE Studie Leiden om de relatie te onderzoeken tussen bloeddruk enerzijds en symptomen van apathie (gemeten met de *Apathy Scale*) en depressieve symptomen (gemeten met de GDS-15) anderzijds. We toonden aan dat een lagere systolische en diastolische bloeddruk gerelateerd waren aan meer symptomen van apathie bij oudere mensen die gebrekkiger functioneerden in het dagelijks leven, terwijl bloeddruk niet gerelateerd was aan apathie bij oudere mensen die beter functioneerden in het dagelijks leven. Bloeddruk was bovendien niet gerelateerd aan depressieve symptomen in de onderzochte subgroepen.
In **hoofdstuk 5** gebruikten we data van de MRI sub-studie van de DANTE Studie Leiden om aan te tonen dat er bij oudere mensen met meer CSVD een relatie was tussen lagere systolische en diastolische bloeddruk en symptomen van apathie, maar niet bij oudere mensen met minder CSVD. In de gehele studiepopulatie noch in de onderzochte subgroepen was bloeddruk gerelateerd aan depressieve symptomen.
In **hoofdstuk 6** lieten we zien dat in de AGES-Reykjavik Studie onder de algemene bevolking, een lagere systolische bloeddruk geassocieerd was met meer depressieve symptomen zoals gemeten met de GDS-12D. Er was geen duidelijke associatie

tussen systolische bloeddruk en cognitieve functie. In de gehele studiepopulatie was bloeddruk niet gerelateerd aan apathie, zoals gemeten met de GDS-3A. Bij stratificatie voor de aanwezigheid van CSVD bleek lagere bloeddruk wel geassocieerd met symptomen van apathie bij deelnemers met meer CSVD. De relatie tussen bloeddruk enerzijds en depressieve symptomen en cognitieve functie anderzijds, werd niet beïnvloed door de hoeveelheid CSVD. De resultaten van dit onderzoek dragen bij aan het de hypothese dat cognitief dysfunctioneren, depressieve symptomen, en symptomen van apathie op latere leeftijd verschillende risicoprofielen hebben.

In **hoofdstuk 7** worden de belangrijkste bevindingen van dit proefschrift besproken. We plaatsen onze bevindingen in het licht van de bestaande literatuur en bediscussiëren de methodologisch sterke en zwakke punten. We stellen hypotheses voor die onze bevindingen kunnen verklaren en doen aanbevelingen voor de klinische praktijk en voor toekomstig wetenschappelijk onderzoek.

Concluderend tonen we in dit proefschrift aan dat cardiovasculaire risicofactoren belangrijk zijn voor neurocognitief functioneren op latere leeftijd. Bovendien laten we zien dat cardiovasculaire determinanten zoals bloeddruk en hs-cTnT op verschillende manieren gerelateerd zijn aan apathie, depressie en cognitief dysfunctioneren.

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Curriculum vitae

Anne Suzanne Bertens (1988) was born in Zutphen, the Netherlands. After graduating high school at the Vrije School de Berkel (Zutphen), she started medical school at Utrecht University (2006). During her Bachelor studies she completed the CRU2006 Honors Program at the Neurology Department at the University Medical Center Utrecht. At the end of her Masters studies she did a research internship with prof. dr. Roos van der Mast and dr. Ton de Craen at the Leiden University Medical Center (LUMC), collecting data for the DANTE Study Leiden. After graduating *cum laude* in 2013, Anne Suzanne obtained a PhD position within the research profile *Aging* at the LUMC, a joint PhD project of the departments of Radiology, Psychiatry, and Geriatrics&Gerontology. After data collection for the DANTE Study Leiden was completed, she was one of the lead PhD students involved in the data collection for the multicenter Heart-Brain Study. During her PhD she followed Epidemiologist B courses and was a visiting scholar (6 weeks) at the National Institute on Aging/ National Institute of Health (Bethesda, Maryland, USA). In 2017, Anne Suzanne started as a psychiatry resident at the LUMC specializing in old age psychiatry, combining clinical work with finishing her PhD research. Anne Suzanne lives in Leiden with her husband David and their son, Olivier.

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