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

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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.

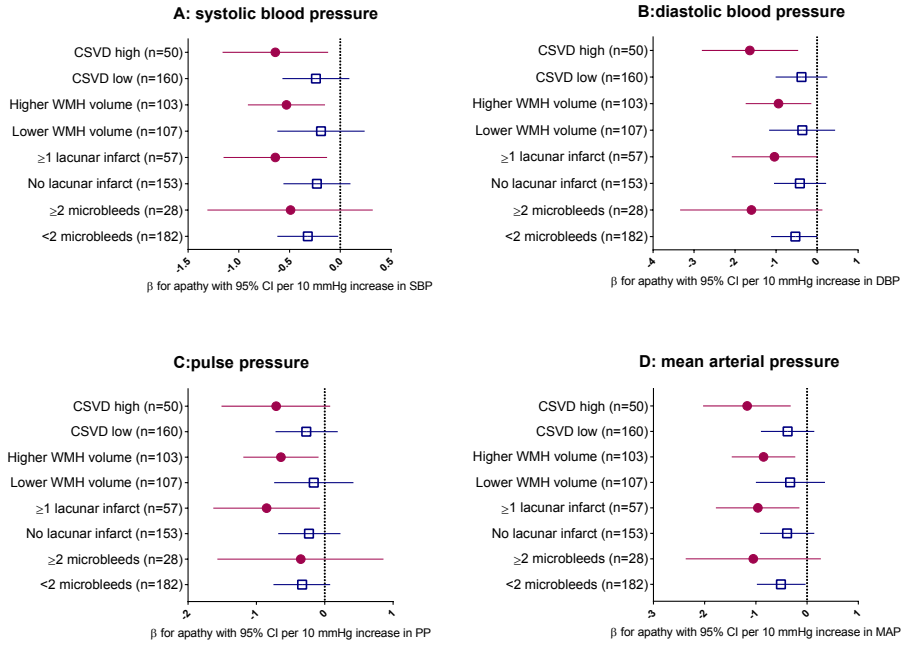

Figure 5.1 Association between blood pressure parameters and symptoms of apathy in strata of different features of cerebral small vessel disease

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.

References

1. Leroi I, Harbishettar V, Andrews M, McDonald K, Byrne EJ, Burns A. Carer burden in apathy and impulse control disorders in Parkinson's disease. International journal of geriatric psychiatry 2012;27:160-166.
2. Carlier A, van Exel E, Dols A, et al. The course of apathy in late-life depression treated with electroconvulsive therapy; a prospective cohort study. International journal of geriatric psychiatry 2018;33:1253-1259.
3. Onyike CU, Sheppard JM, Tschanz JT, et al. Epidemiology of apathy in older adults: the Cache County Study. The American journal of geriatric psychiatry 2007;15:365-375.
4. van Dalen JW, Moll van Charante EP, Nederkoorn PJ, van Gool WA, Richard E. Poststroke apathy. Stroke 2013;44:851-860.
5. Grool AM, Geerlings MI, Sigurdsson S, et al. Structural MRI correlates of apathy symptoms in older persons without dementia: AGES-Reykjavik Study. Neurology 2014;82:1628-1635.
6. Van der Mast RC, Vinkers DJ, Stek ML, et al. Vascular disease and apathy in old age. The Leiden 85-Plus Study. International journal of geriatric psychiatry 2008;23:266-271.
7. Eurelings LS, van Dalen JW, Ter Riet G, Moll van Charante EP, Richard E, van Gool WA. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data. Clinical epidemiology 2018;10:363-379.
8. Moonen JE, de Craen AJ, Comijs HC, Naarding P, de Ruijter W, van der Mast RC. In depressed older persons higher blood pressure is associated with symptoms of apathy. The NESDO study. International psychogeriatrics 2015;27:1485-1493.
9. Moonen JE, Bertens AS, Foster-Dingley JC, et al. Lower Blood Pressure and Apathy Coincide in Older Persons with Poorer Functional Ability: The Discontinuation of Antihypertensive Treatment in Elderly People (DANTE) Study Leiden. J Am Geriatr Soc 2015;63:112-117.
10. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
11. Craig AH, Cummings JL, Fairbanks L, et al. Cerebral blood flow correlates of apathy in Alzheimer disease. Archives of neurology 1996;53:1116-1120.
12. Muller M, Smulders YM, de Leeuw PW, Stehouwer CD. Treatment of Hypertension in the Oldest Old: A Critical Role for Frailty? Hypertension 2013;63:433-441.
13. Moonen JEF, Foster-Dingley JC, De Ruijter W, et al. Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning-the DANTE Study Leiden: A Randomized Clinical Trial. JAMA Internal Medicine 2015;175:1622-1630.
14. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. The Journal of neuropsychiatry and clinical neurosciences 1992;4:134-139.
15. Foster-Dingley JC, Moonen JE, van den Berg-Huijsmans AA, et al. Lower Blood Pressure and Gray Matter Integrity Loss in Older Persons. J Clin Hypertens 2015;17:630-637.
16. Woolrich MW, Jbabdi S, Patenaude B, et al. Bayesian analysis of neuroimaging data in FSL. NeuroImage 2009;45:S173-186.
17. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. The Lancet Neurology 2009;8:165-174.
18. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. The Lancet Neurology 2013;12:483-497.
19. van Sloten TT, Sigurdsson S, van Buchem MA, et al. Cerebral Small Vessel Disease and Association With Higher Incidence of Depressive Symptoms in a General Elderly Population: The AGES-Reykjavik Study. The American journal of psychiatry 2015;172:570-578.
20. Greenberg SM, Charidimou A. Diagnosis of Cerebral Amyloid Angiopathy: Evolution of the Boston Criteria. Stroke 2018;49:491-497.
21. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. Journal of psychiatric research 1982;17:37-49.
22. Bertens AS, Moonen JE, de Waal MW, et al. Validity of the three apathy items of the Geriatric Depression Scale (GDS-3A) in measuring apathy in older persons. International journal of geriatric psychiatry 2017;32:421-428.

23. Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. Soc Sci Med 1996;43:1601-1610.
24. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 1975;12:189-198.
25. Foster-Dingley JC, van der Grond J, Moonen JE, et al. Lower Blood Pressure Is Associated With Smaller Subcortical Brain Volumes in Older Persons. American journal of hypertension 2015;28:1127-1133.
26. Miller LM, Peralta CA, Fitzpatrick AL, et al. The role of functional status on the relationship between blood pressure and cognitive decline: the Cardiovascular Health Study. Journal of hypertension 2019;37:1790-1796.
27. Ogliari G, Sabayan B, Mari D, et al. Age- and Functional Status-Dependent Association Between Blood Pressure and Cognition: The Milan Geriatrics 75+ Cohort Study. J Am Geriatr Soc 2015;63:1741-1748.
28. Muller M, Sigurdsson S, Kjartansson O, et al. Joint effect of mid- and late-life blood pressure on the brain: the AGES-Reykjavik study. Neurology 2014;82:2187-2195.
29. Lanctôt KL, Agüera-Ortiz L, Brodaty H, et al. Apathy associated with neurocognitive disorders: Recent progress and future directions. Alzheimer's & Dementia 2017;13:84-100.
30. Shi Y, Thrippleton MJ, Makin SD, et al. Cerebral blood flow in small vessel disease: A systematic review and meta-analysis. Journal of cerebral blood flow and metabolism 2016;36:1653-1667.
31. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovasc Psychiatry Neurol 2012;2012:367516.
32. Zonneveld HI, Loehrer EA, Hofman A, et al. The bidirectional association between reduced cerebral blood flow and brain atrophy in the general population. Journal of cerebral blood flow and metabolism 2015;35:1882-1887.
33. Alosco ML, Gunstad J, Jerskey BA, et al. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. Brain Behav 2013;3:626-636.
34. van Bemmel T, Holman ER, Gussekloo J, Blauw GJ, Bax JJ, Westendorp RG. Low blood pressure in the very old, a consequence of imminent heart failure: the Leiden 85-plus Study. Journal of human hypertension 2009;23:27-32.
35. Caplan LR. Cardiac encephalopathy and congestive heart failure: a hypothesis about the relationship. Neurology 2006;66:99-101.
36. Hooghiemstra AM, Bertens AS, Leeuwis AE, et al. The Missing Link in the Pathophysiology of Vascular Cognitive Impairment: Design of the Heart-Brain Study. Cerebrovascular diseases extra 2017;7:140-152.