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

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Chapter 6

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

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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).

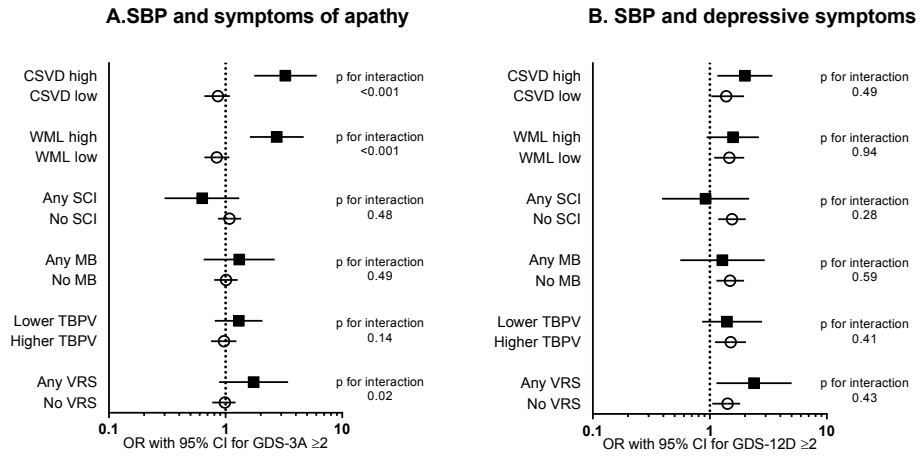

Figure 6.1 Relation between SBP and symptoms of apathy and depressive symptoms according to presence of features of cerebral small vessel disease

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

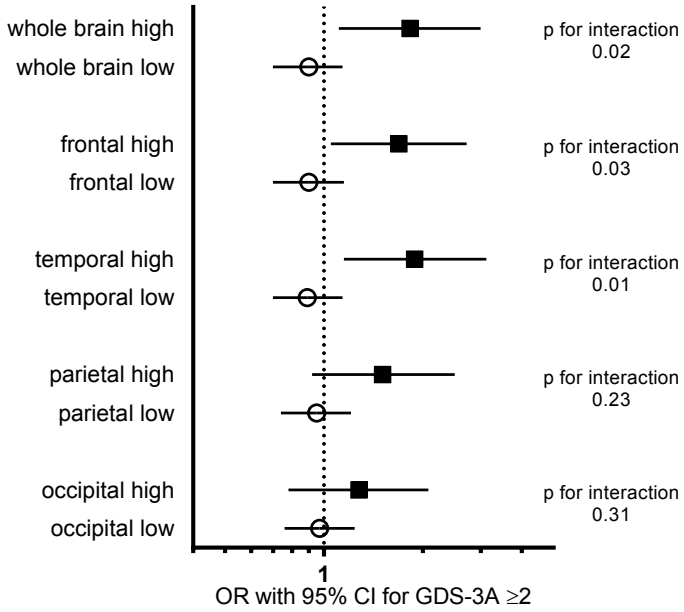

Figure S6.1 Relation between lower SBP and symptoms of apathy according to regional white matter lesion load

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