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

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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

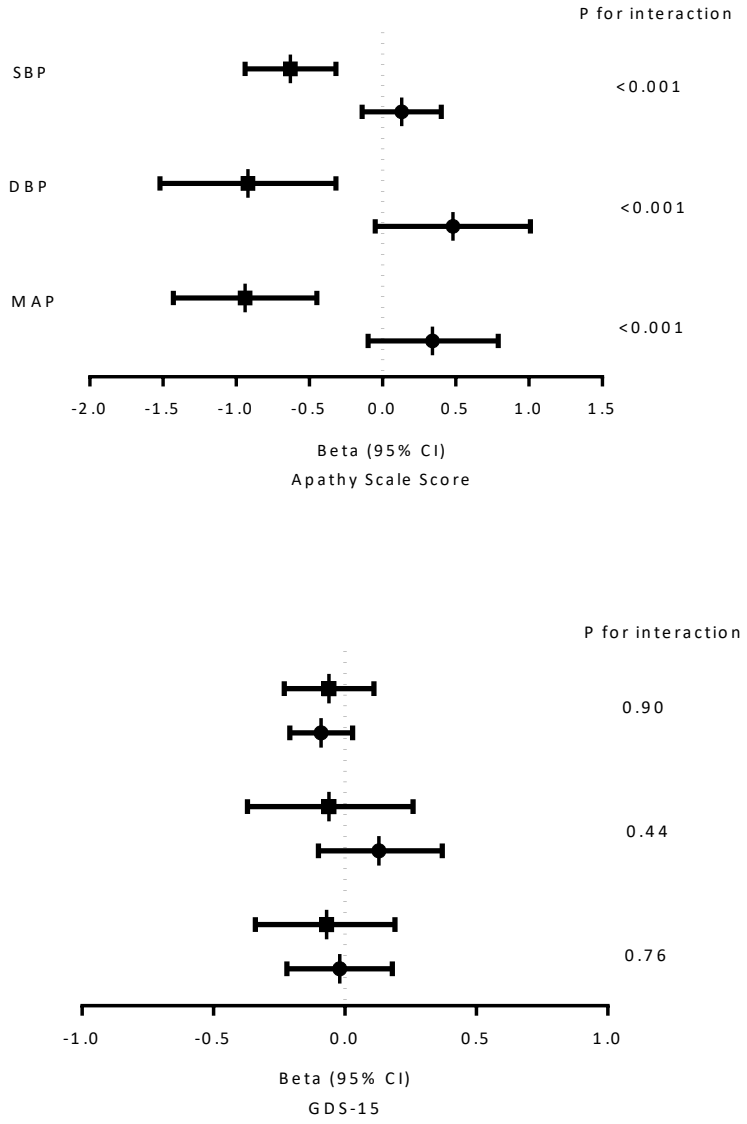

Figure 4.1 Association between blood pressure and symptoms of apathy and depression according to level of functional ability

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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