Perspectives on treating hypertension in old age : the burden of polypharmacy, risks of treatment and GPs' treatment probability

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Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old – data from the Leiden 85-plus Study

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ABSTRACT

Background

The appropriateness of lowering systolic blood pressure remains controversial in the oldest-old. We tested whether systolic blood pressure is associated with all-cause mortality and change in cognitive function for patients prescribed antihypertensive treatment and those without treatment.

Methods

We studied participants in the population-based Leiden 85-plus cohort study. Baseline systolic blood pressure and use of antihypertensive treatment were predictors; all-cause mortality and change in cognitive function measured using the Mini-Mental State Examination were the outcomes. Grip strength was measured as a proxy for physical frailty. We used Cox proportional hazards and mixed-effects linear regression models to analyse the relationship between systolic blood pressure and both time to death and change in cognitive function. In sensitivity analyses we excluded deaths within one year and restricted analyses to participants without a history of cardiovascular disease.

Results

Of 570 participants, 249 (44%) were prescribed antihypertensive therapy. All-cause mortality was higher in participants with lower blood pressure prescribed antihypertensive treatment (HR 1.29 per 10mmHg lower systolic blood pressure, 95% CI 1.15-1.46, $p<0.001$). Participants taking antihypertensives showed an association between accelerated cognitive decline and lower blood pressure (annual mean change -0.35 points per 10mmHg lower systolic blood pressure, 95% CI -0.60, -0.11, $p=0.004$); decline in cognition was more rapid in those with lower handgrip strength. In participants not prescribed antihypertensive treatment, no significant associations were seen between blood pressure and either mortality or cognitive decline.

Conclusions

Lower systolic blood pressure in the oldest-old taking antihypertensives was associated with higher mortality and faster decline in cognitive function.

INTRODUCTION

Hypertension is the most important preventable cause of cardiovascular disease (CVD), including stroke and myocardial infarction [1]. The prevalence of hypertension increases sharply with age [2]. It has been clear for at least two decades that older patients (>60 years) also benefit from antihypertensive treatment [3, 4], but guidelines may not apply equally to everyone over 60 years. For example, we do not know if the effects of treating hypertension are similar among individuals aged over 80 years (the oldest-old) – a segment of the population that is expected to triple in the next two decades [5].

Hypertension studies have tended to exclude patients with multimorbidity and frailty. These criteria disproportionately exclude the oldest-old because this age group are much more likely to have multimorbidity or to be frail [6, 7]. At the same time, observational studies have raised concerns about associations between low systolic blood pressure (SBP), increased mortality and accelerated cognitive decline, especially in the oldest-old living with frailty [8]. Studying associations between SBP and cognitive decline is challenging [9]. There is evidence that high SBP in midlife damages cerebral vessels and impairs brain function [10], but low SBP in late life, particularly in frail subjects, is associated with higher risk for cognitive decline [11]. A study by Mosello *et al.* found that lower SBP was associated with faster cognitive decline in individuals who were already cognitively impaired [12]; several other studies had produced similar findings [13-19]. Mosello *et al.* were the first to describe that antihypertensive therapy modified these associations: low SBP was associated with cognitive decline only in patients under antihypertensive therapy, but not in those who were not prescribed antihypertensive therapy. Unfortunately, the follow-up time was too short to detect long-term protective effects of antihypertensive treatment, and the population was limited to patients attending a memory clinic.

There is therefore a need for rigorous, population-based observational studies with adequate follow up time to test the association between antihypertensive therapy, blood pressure, mortality and cognitive decline in the oldest-old. We analysed data from a population-based cohort study with a five-year follow-up to test if the association between low SBP with all-cause mortality and cognitive function differs for oldest-old patients under antihypertensive treatment and those without treatment, and to test if frailty modifies these associations.

METHODS

Study design and setting

We analysed data from a prospective, population-based cohort study with a five-year follow up - the Leiden 85-plus Study [20, 21]. All inhabitants of the city of Leiden, the Netherlands, were invited to join this cohort study if they turned 85 years between 1997-1999. No exclusion criteria were applied. The target population was 705 inhabitants. Of these, 14 (2.0%) died before being enrolled in the study; 599 (85.0%) provided informed or proxy consent [22]. The Medical Ethical Committee of the Leiden University Medical Center approved the original study.

Participants

For this analysis, we applied two prespecified exclusion criteria. To lower the risk of reverse causality between SBP and mortality risk, we excluded participants who died less than 3 months after they entered the cohort (n=5). We also excluded participants who had no SBP measurements at baseline (n=24).

Procedures and measurements

A history of cardiovascular disease (i.e. previously recorded diagnoses of angina pectoris, myocardial infarction, heart failure, intermittent claudication, peripheral arterial surgery, transient ischaemic attack, and stroke) was available from General practitioners (GPs) or nursing home physicians. At baseline, research nurses visited all participants to administer the Mini-Mental State Examination (MMSE) [23]. At baseline, SBP was measured twice with a mean time range between measurements of 2 weeks. SBP was measured using a mercury sphygmomanometer, in the seated position after at least 5 min of rest and with no vigorous exercise in the preceding 30 min. For this analysis, we averaged the two measurements of SBP. The research nurses also recorded socio-demographic characteristics (level of education, income, living place); current smoking status (yes/no); depressive symptoms if MMSE was >18 points using the 15-point Geriatric Depression Scale [24]; and hand grip strength using a hand dynamometer. During annual follow-up visits, nurses repeated MMSE measurements. All participants were followed for all-cause mortality for 5 years using municipal records.

Statistical Analysis

We assessed associations between exposure (baseline SBP and use of antihypertensive medication) and outcomes (all-cause mortality and annual change in cognitive function) over 5 years. At baseline, we compared characteristics of participants prescribed and not prescribed antihypertensive therapy. The crude and adjusted modelling approaches for all-cause mortality using Cox proportional hazard models and annual change in MMSE using mixed-effects linear regression models are described in detail in Appendix text. Subgroup analyses were

performed for the second aim, to test if grip strength (as a proxy for frailty) modified the associations of SBP and treatment with the outcomes. We stratified both models for low/high hand grip strength to explore effect sizes and directions of effects. However, due to small sample sizes, this subgroup analysis was only exploratory. In sensitivity analyses, we firstly excluded deaths within 1 year after baseline; secondly restricted the models to participants without a history of CVD at baseline; and thirdly recoded participants who could not perform the hand grip strength test as missing. A two-sided P-value of 0.05 was taken as statistically significant for all analyses. We used STATA 15.0 (StataCorp, College Station, TX, USA) for all analyses.

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RESULTS

We analysed data from 570 individuals, of whom 249 (43.7%) were prescribed antihypertensive therapy at baseline (Table 1). Participants prescribed antihypertensive therapy and those not prescribed antihypertensives were similar in all aspects except for a higher prevalence of CVD in those prescribed antihypertensives (61.9% vs. 35.8%, p<0.001). The other cardiovascular, socio-demographic, and functional characteristics at baseline were equally distributed among the two groups.

Appendix table 1 describes the sample of 214 participants grouped in lowest/highest SBP quintile. In the group prescribed antihypertensive therapy, participants with SBP <140 mmHg were more often institutionalized than those with SBP >170 mmHg (33.3% vs. 4.7%, p=0.001), and had slightly lower baseline MMSE (median 26 vs. median 27, p=0.021). The same pattern was evident in participants not prescribed antihypertensive therapy.

All-cause mortality over time

Figure 1 shows Kaplan-Meier survival curves for participants in the highest and lowest quintiles of SBP. Those prescribed antihypertensive therapy with SBP >170 mmHg had the lowest risk of all-cause mortality, and those with SBP <140mmHg had the highest risk (log rank test p<0.001).

During the 5-year follow-up, 263 (46.1%) participants died. For those participants prescribed antihypertensive therapy, all-cause mortality was significantly higher with decreasing SBP (HR 1.29 per 10mmHg lower SBP, 95%CI 1.15-1.46, p<0.001) (Table 2). For those not prescribed antihypertensives, the effect was smaller and did not reach significance (HR 1.08 per 10mmHg

Table 1. Baseline characteristics of participants at age 85 years by antihypertensive treatment (*n*=570).

Domains	Overall (*n*=570)	Antihypertensive treatment (*n*=249)	No antihypertensive treatment (*n*=321)	P-value[a]
Sociodemographic characteristics				
Women, n (%)	380 (66.7)	173 (69.5)	207 (64.5)	0.21
Low education[b], n (%)	358 (64.9)	163 (66.8)	195 (63.3)	0.39
Low income[c], n (%)	280 (50.9)	122 (50.8)	158 (51.0)	0.98
Institutionalized, (%)	102 (18.4)	45 (18.4)	57 (18.3)	0.97
Cardiovascular characteristics				
SBP in mmHg, mean (SD)[d]	155.2 (18.7)	154.8 (16.8)	155.5 (20.0)	0.64
Current Smoker, n (%)	89 (15.7)	33 (13.3)	56 (17.6)	0.16
Diabetes mellitus, n (%)	91 (16.3)	46 (18.9)	45 (14.2)	0.14
CVD[e], n (%)	269 (47.2)	154 (61.9)	115 (35.8)	<0.001
Functional characteristics				
Cognition (MMSE [f]), median (IQR)	26 (22-28)	26 (21-28)	26 (23-28)	0.094
Depression (GDS[g]), median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	0.70
Low hand grip strength[h], n (%)	362 (63.5)	161 (64.7)	201 (62.6)	0.62

[a] Chi-square test for categorical variables, t-test for normally distributed continuous and Wilcoxon rank-sum test for non-normally distributed data was used

[b] defined as primary school only

[c] defined as state pension only (about EUR 750 monthly)

[d] SBP = systolic blood pressure was measured twice during home visit at baseline in a seated position, two weeks apart, and after at least 5 minutes of rest and no vigorous exercise in the preceding 30 minutes. Both measurements were averaged.

[e] CVD included angina pectoris, myocardial infarction, heart failure, intermittent claudication, peripheral arterial surgery, TIA, and stroke

[f] MMSE, possible scores range from 0 to 30 points (worst to best). Missing data in n=7.

[g] GDS-15, possible scores range from 0-15 (worst to best). Data not available for participants with Mini-Mental State Examination (MMSE) scores <18 (n=97).

[h] Participants with hand grip strength below the sex-specific medians or unable to perform the test (n=35)

lower SBP, 95% 1.00-1.18, p=0.057). The sensitivity analyses returned similar results in the model excluding deaths (n=47) within 1-year after baseline (Appendix table 2) and when the model was restricted to participants with no history of CVD at baseline.

Change of cognitive function over time

Figure 2 describes the median annual change in MMSE for those in the highest and lowest quintiles of SBP, both for those prescribed antihypertensives and those not prescribed antihypertensives. In the group prescribed antihypertensives, those with SBP in the lowest quintile showed faster cognitive decline compared to those in the highest SBP-quintile (-1.1 points per year [IQR 1.4] vs -0.1 points per year [IQR 0.6]; p=0.022). For those not prescribed

antihypertensive therapy, no significant difference between the lowest and highest quintiles of blood pressure was evident (-0.7 points per year [IQR 2.2] vs. -0.5 points per year [IQR 1.4]; p=0.46).

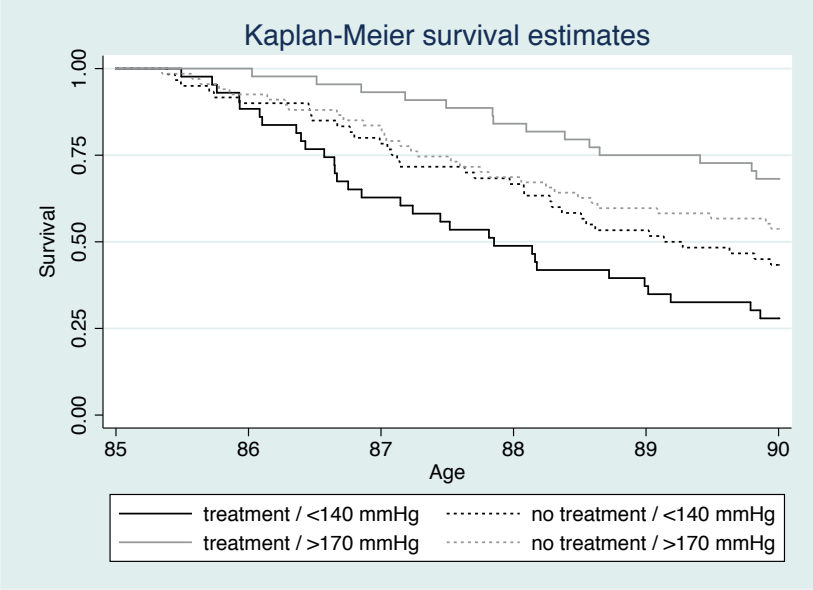

Figure 1. Kaplan-Meier survival curves for all-cause mortality grouped by under/without antihypertensive therapy and lowest/highest quintile of systolic blood pressure. All participants were aged 85 years when included in the study and followed-up to a maximum of 5 years.

Table 2. Subgroup analysis for hand grip strength and associations of systolic blood pressure (SBP) and all-cause mortality per 10 mmHg lower SBP (n=570)

		Hazard ratio (95% CI) per 10 mmHg lower SBP	P-value
Treatment			
Overall[a] *(n=249)*		*1.29 (1.15, 1.46)*	*<0.001*
By hand grip strength[b]	Low (n=161)	1.24 (1.08, 1.42)	0.002
	High (n=88)	1.40 (1.09, 1.80)	0.009
No treatment			
Overall[a] *(n=321)*		*1.08 (1.00, 1.18)*	*0.057*
By hand grip strength[b]	Low (n=201)	1.10 (1.00, 1.21)	0.060
	High (n=120)	0.99 (0.86, 1.15)	0.90

[a] Participants during and without antihypertensive treatment, adjusted for sex and cardiovascular disease

[b] Participants who were unable to perform the test (n=35) were classified to be low in hand grip strength, adjusted for sex and cardiovascular disease

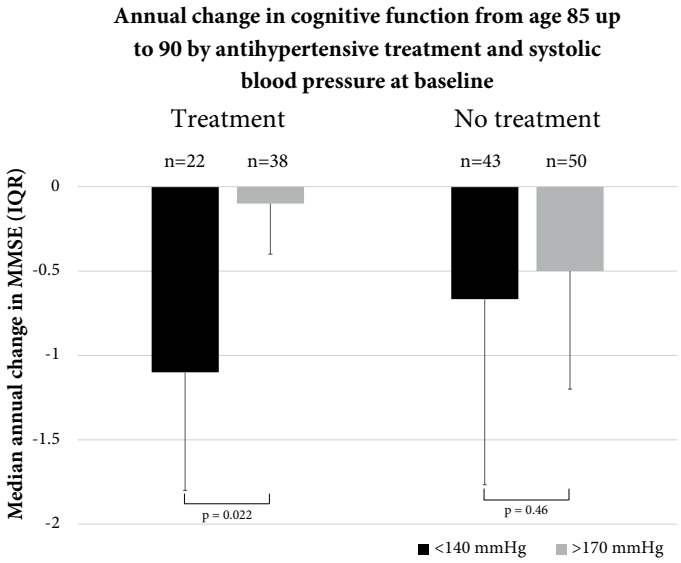

Figure 2. Annual change in cognitive function (measured by the Mini-Mental State Examination, MMSE) grouped by under/without antihypertensive therapy and lowest/highest quintile of systolic blood pressure.

After accounting for baseline differences, those prescribed antihypertensives showed a faster rate of decline in MMSE with lower blood pressure (annual change in MMSE of -0.35, 95% CI -0.60 to -0.11 per 10mmHg drop in SBP; p=0.004). For those not prescribed antihypertensive therapy, the rate of decline was not significantly faster with lower baseline blood pressure (annual change in MMSE -0.14, 95% CI -0.39 to 0.11 per 10mmHg drop in SBP; p=0.28) (Table 3). The sensitivity analysis returned similar results when the model was restricted to participants with no history of CVD at baseline.

Modification by frailty

Our results did not change in our subgroup analyses for all-cause mortality (Table 2), when we stratified by low or high hand grip strength in participants prescribed antihypertensive therapy (p for interaction=0.28) or not prescribed antihypertensive therapy (p for interaction=0.29). There was weak evidence for an association in those participants not prescribed antihypertensives who had low hand grip strength (HR 1.10, 95% CI 1.00 to 1.21, p=0.060).

The subgroup analyses for annual change in cognitive function (Table 3) showed that accelerated change in MMSE with lower SBP was significant for those under antihypertensive therapy when they had low hand grip (annual change in MMSE -0.37, 95% CI -0.70 to -0.05 per 10mmHg drop in SBP; p=0.023) but did not reach significance for those with high hand grip strength (annual change in MMSE -0.24, 95% CI -0.57 to 0.09 per 10mmHg drop in SBP;

Table 3. Subgroup analysis for hand grip strength and changes in cognitive function measured by the Mini-Mental State Examination (MMSE) according to systolic blood pressure (SBP) at age 85 (per 10 mmHg lower SBP).

		Baseline difference		Annual change		Accelerated change	
		Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Treatment							
Overall[a] *(n=220)*		*-0.33 (-0.63, -0.03)*	*0.032*	*+1.20 (-0.50, +2.91)*	*0.17*	*-0.35 (-0.60, -0.11)*	*0.004*
By hand grip strength[b]	Low (n=141)	-0.38 (-0.78, +0.02)	0.061	+1.14 (-1.18, +3.45)	0.34	-0.37 (-0.70, -0.05)	0.023
	High (n=79)	-0.04 (-0.47, +0.39)	0.84	+0.87 (-1.30, +3.05)	0.43	-0.24 (-0.57, +0.09)	0.15
No treatment							
Overall[a] *(n=284)*		*-0.72 (-1.00, -0.44)*	*<0.001*	*-0.62 (-2.39, +1.16)*	*0.50*	*-0.14 (-0.39, +0.11)*	*0.28*
By hand grip strength[b]	Low (n=172)	-0.80 (-1.20, -0.40)	<0.001	-0.90 (-3.60, +1.79)	0.51	-0.13 (-0.49, +0.24)	0.50
	High (n=112)	-0.18 (-0.49, +0.12)	0.23	-0.76 (-2.13, +0.61)	0.28	-0.04 (-0.24, +0.17)	0.74

'Baseline difference' means the association per 10 mmHg lower SBP and MMSE at baseline. 'Annual change' indicates the annual difference in MMSE over time until age 90. 'Accelerated change' is the additional change in MMSE over time associated per 10 mmHg lower SBP.

[a] Participants with and without antihypertensive treatment, adjusted for sex and cardiovascular disease

[b] Participants unable to perform the test (n=35) were classified to have less hand grip strength, adjusted for sex and cardiovascular disease

p=0.15). There was no evidence of interaction of hand grip strength in those without therapy (p for interaction=0.10). The sensitivity analysis returned similar results when participants who could not perform the hand grip strength test were classified as missing data instead of categorized as having low hand grip strength.

DISCUSSION

In this population-based cohort of individuals aged 85 years with a 5-year follow-up, we found lower SBP was associated with higher all-cause mortality and faster annual cognitive decline in participants prescribed antihypertensive therapy. In participants without antihypertensive treatment, no relation was found between SBP and mortality or cognitive decline. Low grip strength did not modify the association of SBP and mortality but did for cognitive decline.

Our findings are in line with other cohort studies showing the same associations of low SBP and increased mortality although previous analyses did not stratify for antihypertensive treatment [25, 26]. For cognition, age seems to modify the associations; in studies with patients aged >60 there was either no association between SBP and cognitive decline [27] or an association of higher SBP with a lower risk of dementia [28]. At age 85 years and older, low SBP predicts the onset of dementia [15] and is associated with worse cognitive function [17].

Similarly, a cohort of male participants whose SBP trajectories were followed over 32 years showed that those who develop dementia had a greater increase in SBP followed by a decrease in SBP compared to those who did not develop dementia [29]. These findings could explain the accelerated cognitive decline we found in our patients with low SBP under antihypertensive treatment. Our results are also in line with Mosello *et al.'s* findings [12] where 172 patients with a mean age of 79 years, taking antihypertensive therapy, and with a diagnosis of dementia or mild cognitive impairment of outpatient memory clinics were followed-up for a median of 9 months. Our results confirm and extend these findings by showing similar associations in a population-based cohort over a longer observation period of 5 years.

This cohort study has several strengths. The population-based sample included a large number of participants, extensive measurements and high follow up rates with a low risk for selection bias. The inclusion of participants from nursing homes further enhances the generalisability of the findings.

This is an observational study, with all the limitations that implies. However, it is useful to look at the associations we identified by situating them within the GRADE framework and apply the Bradford Hill's criteria for causation because 'observational studies may provide more relevant information than RCTs' [30]. The strength of association we found, consistency with prior studies, and the dose-response relationship in our study are three of these criteria. In addition, this study established a temporal relationship between SBP values measured at baseline and outcome assessments over 5 years. Our sensitivity analysis showed robust results when we excluded deaths within 1 year after baseline, which reduces, but does not exclude, the risk that our findings are due to reverse causality.

We acknowledge further limitations. First, there was no SBP measurement at baseline for about 5% of participants. Excluding these participants is unlikely to introduce bias as the numbers are small. Second, the risk for confounding by indication limits the causal interpretation of our associations. Interpretation of the results is helped by the findings of a large international study including >2500 GPs [31], which may allow us to understand and adjust for factors (for example frailty) that influence GPs' decision to start or not start antihypertensive therapy in the oldest-old. Third, if participants are prescribed with antihypertensive therapy but did not adhere to treatment, misclassification bias could be introduced. However, Dutch individuals seem to adhere best to therapy compared to seven other countries [32], and this high level of adherence reduces the risk of such bias in our sample.

Despite these limitations, the finding that low SBP is associated with increased mortality and cognitive decline in oldest-old under antihypertensive therapy is concerning. For clinicians, this study raises the question of what the optimal target blood pressure level is for 85-year-

oldm frail patients. We support the suggestions from Benetos *et al.* [33] to follow an individualized approach when treating hypertension in oldest-old >80 years with frailty, due to the lack of evidence [6, 34]. Observational studies remain at risk for bias (i.e. reverse causality, residual confounding), and the way to provide more evidence could be via deprescribing trials to test effectiveness and safety of lowering or removing antihypertensive therapy. The Dutch DANTE trial used this approach over a 16-week period in patients aged 75 and older with mild cognitive impairment [35]. In DANTE, deprescribing was not beneficial but was safe. Future studies should try to recruit patients that could benefit the most from deprescribing such as individuals with frailty and/or limited life expectancy.

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Appendix text – detailed plan of analysis

We assessed associations between exposure (level of SBP with/without antihypertensive therapy) and outcomes (all-cause mortality/annual change in cognitive function) over 5 years.

Missing data was handled two ways: 1) We excluded participants with missing information on baseline SBP (n=24, 4%) and potential confounders (n=3-20, 1%-3%, income was the variable with most [n=20] missing data). 2) We grouped participants who were unable to perform the hand grip strength test (n=35, 6%) in the group of lower than median hand grip strength.

Our descriptive analysis compared baseline characteristics in those with/without antihypertensive treatment. Chi-square tests were performed for categorical variables, t-tests or Wilcoxon rank-sum test for continuous data where appropriate.

In a crude regression model, SBP was first grouped into quintiles. Only participants from the two most extreme quintiles of lowest and highest SBP (<140 and >170 mmHg) were retained. Finally, we re-parameterized both exposure variables (SBP and antihypertensive therapy) into a new categorical variable, with four sub-categories (2 levels of SBP by 2 levels of treatment) so we could visually explore associations of both exposure variables and each outcome at once. We then presented all-cause mortality in crude Kaplan-Meier time-to-event curves for each of the four groups. Groups (SBP/treatment) were compared with log-rank tests. Next, we grouped SBP in 10mmHg units for all participants. We found no evidence for a significant departure from linear trend (tested with Likelihood ratio test [LRT]).

For all-cause mortality, we used Cox proportional hazards models with SBP as the exposure, testing separately for antihypertensive treatment (yes/no). We tested proportional hazard assumptions and they were all valid. We, a priori, chose sex, and CVD as confounders, and took a causal modelling approach to identify potential confounders to the association of SBP/treatment and the outcomes: living situation, income, education, smoking status, diabetes, and depression (i.e. GDS-score). We calculated crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) and tested the later for multicollinearity. Interaction was only tested as pre-specified for frailty in a subgroup analysis.

Annual change in cognitive function was calculated as the median annual difference and inter-quartile range (IQR) in MMSE for each of the four groups. We then compared estimates and IQR for low and high SBP, using Wilcoxon rank-sum tests separately for participants with/without antihypertensive treatment. While this approach did not account for correlated data (i.e. multiple measurements per participant), we later used a mixed-effects linear regression models that account for the clustering within each participant as a random effect [25].

The models provided estimates for 'SBP', 'year' (of follow-up) and 'SBP * year'. The estimate for 'SBP' indicated the baseline difference in MMSE per 10mmHg lower SBP (presented in Table 3 as 'baseline difference'). The estimate for 'year' indicated the annual change in MMSE (presented in Table 3 as 'annual change'). The estimate for 'SBP * year' indicates the accelerated change in MMSE per year per 10mmHg lower SBP (presented in Table 3 as 'accelerated decline').

Subgroup analyses were performed for the second aim, to see if frailty modified the associations of SBP/treatment with the outcomes. We stratified both models for low/high hand grip strength to explore effect sizes and directions of effects. We tested for interaction using LRT. However, due to small sample sizes, this subgroup analysis was only exploratory.

A two-sided P-value of 0.05 was statistically significant. We used STATA 15.0 (StataCorp, College Station, TX, USA) for all analyses.

Appendix table 1. Subgroup of participants with baseline systolic blood pressure (SBP) at baseline of <140 mmHg (lowest quintile) and >170 mmHg (highest quintile) stratified by antihypertensive treatment (*n*=214).

Domains	Antihypertensive treatment		P-value[a]	No antihypertensive treatment		P-value[a]
	<140 mmHg (*n*=43)	>170 mmHg (*n*=44)		<140 mmHg (*n*=60)	>170 mmHg (*n*=67)	
Sociodemographic characteristics						
Women, n (%)	30 (69.8)	32 (72.7)	0.76	40 (66.7)	41 (61.2)	0.52
Low education[b], n (%)	26 (66.7)	31 (72.1)	0.59	39 (66.1)	45 (69.2)	0.71
Low income[c], n (%)	18 (47.4)	16 (37.2)	0.36	32 (54.2)	32 (50.0)	0.64
Institutionalized, (%)	13 (33.3)	2 (4.7)	0.001	23 (38.3)	6 (9.2)	<0.001
Cardiovascular characteristics						
Current Smoker, n (%)	2 (4.7)	8 (18.2)	0.089	9 (15.5)	12 (17.9)	0.81
Diabetes mellitus, n (%)	10 (25.6)	5 (11.6)	0.15	14 (23.3)	8 (12.3)	0.16
CVD[d], n (%)	33 (76.7)	26 (59.1)	0.078	25 (41.7)	29 (43.3)	0.86
Functional characteristics						
Cognition (MMSE [e]), median (IQR)	26 (19-27)	27 (23-28)	0.021	23.5 (13-27)	27 (23-28)	0.002
Depression (GDS[f]), median (IQR)	2 (1-4)	2 (1-3)	0.35	2 (1-4)	1 (1-3)	0.17
Low hand grip strength[g], n (%)	32 (74.4)	27 (61.4)	0.19	48 (80.0)	38 (56.7)	0.005

[a] P-values were derived from Chi-square tests for categorical variables, exact Fisher tests (if too few observations per cell expected), and Wilcoxon rank-sum test for continuous not-normally distributed data.

[b] defined as primary school only

[c] defined as state pension only (about EUR 750 monthly)

[d] CVD included angina pectoris, myocardial infarction, heart failure, intermittent claudication, peripheral arterial surgery, TIA, and stroke

[e] MMSE, possible scores range from 0 to 30 points (worst to best). Missing data in n=3.

[f] GDS-15, possible scores range from 0-15 (worst to best). Data not available for participants with Mini-Mental State Examination (MMSE) scores <18 (n=44).

[g] Participants unable to perform the test (n=16) were classified to have low hand grip strength.

Appendix table 2. Sensitivity analysis excluding participants that died within one year after baseline. Subgroup analysis for hand grip strength and associations of systolic blood pressure (SBP) and all-cause mortality per 10 mmHg lower SBP (n=534)

		Hazard ratio (95% CI) per 10 mmHg lower SBP	P-value
Treatment			
Overall[a] (n=235)		*1.25 (1.10, 1.42)*	*0.001*
By hand grip strength[b]	Low (n=150)	1.22 (1.05, 1.41)	0.009
	High (n=85)	1.28 (0.97, 1.67)	0.078
No treatment			
Overall[a] (n=299)		*1.09 (0.99, 1.19)*	*0.074*
By hand grip strength[b]	Low (n=184)	1.11 (0.99, 1.23)	0.069
	High (n=120)	0.99 (0.85, 1.17)	1.00

[a] Participants during and without antihypertensive treatment, adjusted for sex and cardiovascular disease

[b] Participants who were unable to perform the test (n=32) were classified to be low in hand grip strength, adjusted for sex and cardiovascular disease