Chapter 3

Association of visit-to-visit blood pressure variability with cognitive function in old age: a prospective cohort study

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Abstract

Background Visit-to-visit blood pressure variability has been related to cerebrovascular damage. The aim of this study was to assess the association between visit-to-visit blood pressure variability and cognitive function in older subjects.

Methods We included 5,461 subjects from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study. Blood pressure was measured every three months during an average period of 3.2 years. Blood pressure variability was defined as the standard deviation of visit-to-visit blood pressure measurements. Four domains of cognitive function including selective attention, processing speed, immediate and delayed memory were assessed and a compound cognitive score was computed by averaging the four standardized z-scores. In an MRI substudy of 553 participants, structural brain volumes, cerebral microbleeds, infarcts, and white matter hyperintensities were measured.

Results Participants with higher visit-to-visit variability in systolic blood pressure had worse performance on all cognitive tests: attention (mean difference high versus low thirds) 3.08 seconds (95% confidence interval (CI) 0.85 to 5.31), processing speed -1.16 digits coded (95% CI-1.69 to -0.63), immediate memory -0.27 pictures remembered (95% CI -0.41 to -.13), and delayed memory -0.30 pictures remembered (95% CI -0.49 to -0.11). Furthermore, higher variability in both systolic and diastolic blood pressure was associated with lower hippocampal volume and cortical infarcts, and higher variability in diastolic blood pressure was associated with cerebral microbleeds (all p-values<0.05). All associations were adjusted for average blood pressure and cardiovascular risk factors.

Conclusion Higher visit-to-visit variability in blood pressure independent of average blood pressure was associated with impaired cognitive function in old age.

Introduction

Visit-to-visit variability in blood pressure independent of average blood pressure is related to cerebrovascular damage.(1) It has been shown that higher blood pressure variability increases the risk of stroke and that antihypertensives, which decrease both variability in blood pressure and mean blood pressure, more effectively reduce the risk of stroke.(2) In addition, observational studies have shown associations of variability in blood pressure, independent of average blood pressure, with white matter hyperintensities, carotid artery intima media thickness, and atherosclerosis in older people (≥55 years).(3-5)

The relation between increased variability in blood pressure and end organ damage is well established.(6) Recent evidence indicates that higher visit-to-visit variability is linked with microvascular damage, endothelial injury, and disturbances in vascular smooth muscle functioning.(7, 8) Indicators of cerebral small vessel disease, including white matter hyperintensities, cortical microinfarcts, and cerebral microbleeds are implicated in the pathogenesis of cognitive impairment.(9-11) Several pathological, observational, and experimental studies have shown that disruption of the blood-brain barrier due to microvascular damage results in neuronal injury and accelerates neuronal loss and brain atrophy.(12) Hence higher variability in blood pressure might potentially lead to cognitive impairment through changes in the brain structures and development of cerebral small vessel disease.

We investigated the association of variability in blood pressure between visits independent of average blood pressure with cognitive function in older participants (>70 years) at high risk of cardiovascular disease. Additionally, we investigated possible explanations behind this association in a magnetic resonance imaging substudy.

Methods

Study design and participants

The data in this study were obtained from PROSPER (The PROspective Study of Pravastatin in the Elderly at Risk), a randomized, double blind, placebo controlled trial designed to investigate the effect of pravastatin in the prevention of vascular events in elderly people with pre-existing, or risk factors for, cardiovascular disease. This trial included 5,804 people aged 70-82 years who were enrolled from three collaborating centers in Ireland, Scotland, and the Netherlands. Approximately 50% of the participants showed evidence of cardiovascular disease, including stable angina, intermittent claudication, stroke (the type,

hemorrhagic or ischemic, was unknown), transient ischemic attack, myocardial infarction, and vascular surgery. The rest of the participants had one or more major cardiovascular risk factors, defined as hypertension, cigarette smoking, or diabetes mellitus. The primary outcome of the PROSPER study was the combined endpoint of definite or suspected death from coronary heart disease, non-fatal myocardial infarction, and fatal or non-fatal stroke during a mean follow-up period of 3.2 years. In the present study we included 5461 participants for whom data on variability in blood pressure and cognitive function were available. Additionally, participants from the Netherlands were invited to participate in an MRI substudy. Participants were included from both the pravastatin and placebo groups as we previously reported that treatment with pravastatin did not influence cognitive function, structural brain volumes, or indicators of cerebral small vessel disease.(13-15)

Blood pressure measurements

We measured systolic and diastolic blood pressure at baseline and every three months. Blood pressure was measured with participants in the sitting position and using a fully automatic electronic sphygmomanometer (Omron M4, Kyoto, Japan). All measurements were performed in the same clinical setting. In the analyses we used the average values of these blood pressure measurements. We defined visit-to-visit variability in blood pressure as the standard deviation of blood pressure measurements during the study period. We report the variability in blood pressure using only the standard deviation. Variance and coefficient of variation, which are two other measures of variability, are strongly correlated with the standard deviation (supplemental table 1) and they showed similar associations with cognitive and magnetic resonance imaging outcomes (data not shown).

Cognitive function

The Mini-Mental State Examination (MMSE) was used to evaluate global cognitive function at baseline; to exclude participants with poor cognitive function at baseline we used a cut-off score of 24 points or more (out of 30) as an inclusion criterion. In the present study we used data on cognitive function assessed at the end of the study, after a mean follow-up of 3.2 years, by a cognitive test battery consisting of four different tests. The Stroop colour and word test was used to assess selective attention and reaction time. The participants were asked to read the name of a colour, which appeared in a colour different from that being named. The outcome variable was the total number of seconds to complete the test; a higher score indicating worse performance. General cognitive speed was tested by the letter-digit coding test. The participants had to match certain digits with letters according to a provided key. The outcome variable was the total number of correct entries

in 60 seconds, with higher scores indicating better performance. The picture-word learning test was used to assess immediate and delayed memory. The participants were shown 15 pictures and were then asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the test to measure their delayed recall. The outcome variable was the accumulated number of correct recalled pictures, immediately and after 20 minutes, with higher scores indicating better performance. A detailed description of the cognitive tests and the procedures has been published previously.(16)

Magnetic resonance imaging substudy

Overall, 646 of the 1100 Dutch participants in the PROSPER study consented to participate in the magnetic resonance imaging substudy. Forty of the 646 original study participants died during the follow-up period. Magnetic resonance imaging was performed at the end of the follow-up period in the remaining 606 participants. Data on visit-to-visit variability in blood pressure and magnetic resonance imaging were available for 553 participants. Details of individually magnetic resonance imaging scanning have been published previously.(13)

All imaging was performed on a magnetic resonance system operating at a field strength of 1.5 Tesla (Philips Medical Systems, Best, Netherlands). We used the SIENAX technique to calculate grey and white matter volumes. In short, SIENAX starts by extracting brain and skull images from input data for the whole head. The brain image is then affine registered to Montreal Neurological Institute 152 space (by using the skull image to determine the registration scaling), done primarily to obtain the volumetric scaling factor to be used as normalisation for head size. Next we carried out tissue type segmentation with partial volume estimation to calculate the total volume of brain tissue (including separate estimates of volumes of grey matter, white matter, peripheral grey matter, and ventricular cerebrospinal fluid).(17) The algorithm FIRST (the Oxford Centre for Functional MRI of the Brain's (FMRIB) integrated registration and segmentation tool) was applied to estimate the volume of hippocampus. In addition, we estimated the volume of six other subcortical regions, including nucleus accumbens, globus pallidus, amygdala, putamen, caudate nucleus, and thalamus. FIRST is part of FSL (FMRIB's software library) and performs both registration and segmentation of the mentioned subcortical regions.(18) To assess cerebral microbleeds, two experienced raters blinded to the participants' clinical history read all the magnetic resonance imaging scans in consensus. Cerebral microbleeds were defined as focal areas of signal loss on T2 weighted gradient echo pulse sequence ("blooming effect") that were invisible or smaller on T2 weighted magnetic resonance imaging.(19) For each participant we recorded the number and location (cortical, subcortical, and infratentorial) of the cerebral microbleeds. Segmenta-

tion of white matter hyperintensities volume was performed automatically using software for Neuro-Image Processing in Experimental Research (SNIPER), an in-house developed program for image processing.(20) This segmentation was based on the T2-weighted and fluid attenuated inversion recovery (FLAIR) images. Cerebral infarcts were defined as parenchymal defects seen on FLAIR images with the same signal intensity as cerebrospinal fluid and a surrounding rim of high signal intensity following a vascular distribution.

Personal and clinical characteristics

We recorded the personal, medical, and anthropometric data of the participants at baseline. A fasting venous blood sample was taken for biochemical and hematological assessment. Western blotting was used on the plasma samples to determine apolipoprotein E epsilon 2/3/4 phenotype.(21)

Statistical analysis

Characteristics of the study participants are reported as mean (standard deviation) for continuous variables and frequency (percentage) for categorical variables. We used Pearson's correlation coefficient to calculate the correlation between variability in blood pressure and average blood pressure. Linear regression models were used to assess the association of variability in blood pressure and average blood pressure with cognitive function. Dependent variables were the mean scores of the cognitive tests. In the tables these scores are presented in thirds of systolic and diastolic blood pressure and blood pressure variability. In the magnetic resonance imaging substudy, we used logistic regression models to estimate the odds ratio and 95% confidence interval of the presence of microbleeds or infarcts in different thirds of blood pressure variability as well as average blood pressure. We used multivariable linear regression models to test the association between blood pressure variability and average blood pressure with volume of white matter hyperintensities and structural brain volumes. P-values in all the analyses were calculated using systolic and diastolic blood pressure variability as continuous variables.

We performed our analyses in three steps. In the first step, we carried out crude analyses, in which we only adjusted for cognitive test version where appropriate. In the second step, we added age, sex, education, and country as covariates to investigate the potential influence of these factors on the associations (model 1). In the final model (model 2), we further adjusted the analyses for the following potential confounders: cardiovascular diseases and risk factors (history of vascular disease, history of hypertension, history of diabetes mellitus, smoking status, cholesterol levels, body mass index), average blood pressure, statin treat-

ment, and apolipoprotein E genotype. We adjusted the analyses of systolic blood pressure variability with cognitive function and magnetic resonance imaging outcomes for average systolic blood pressure. The analyses of variability in diastolic blood pressure with cognitive function and magnetic resonance imaging outcomes were adjusted for average diastolic blood pressure. Since the associations did not essentially change in different models, results of the second model are presented in the manuscript and results from the other models are presented in a supplementary file (available on request). All analyses were performed using SPSS software (version 20.0.0, SPSS Inc., Chicago, IL).

Results

Table 1 shows the characteristics of participants in the whole group and in the magnetic resonance imaging substudy. Blood pressure was measured in an average number of 12.7 visits in the whole group and 12.9 visits in the magnetic resonance substudy. Average systolic and diastolic blood pressure over the period of blood pressure measurements were 153.1 mm Hg and 82.5 mm Hg, respectively. The corresponding mean standard deviation values during this period were 14.8 mm Hg and 7.1 mm Hg.

There was a weak but significant correlation between average systolic blood pressure and standard deviation of systolic blood pressure measurements ($r=0.20$, p-value<0.001). Similarly, average diastolic blood pressure was weakly but statistically significantly correlated with standard deviation of diastolic blood pressure measurements ($r=0.12$, p-value<0.001).

Table 2 shows the association of visit-to-visit variability in systolic and diastolic blood pressure with cognitive function. Higher variability was associated with worse performance on the Stroop test (both p-values<0.001), letter-digit coding test (both p-values<0.001), immediate picture-word learning test (both p-values<0.001), and delayed picture-word learning test (both p-values$=0.001$). All associations were independent of average blood pressure and cardiovascular diseases and risk factors, as all analyses were adjusted for these factors. The figure presents the mean cognitive scores (95% confidence intervals) in each third of systolic and diastolic blood pressure variability. Data on the association of blood pressure variability with cognitive function from crude and minimally adjusted models are shown in the supplemental tables 2 and 3. Furthermore, we found a significant association of higher average systolic and diastolic blood pressure with worse performance in different domains of cognitive function (all p-values<0.05), except for the association

between higher average systolic blood pressure and performance on the picture-word learning tests (p-values>0.05) (supplementary table 4).

Table 1. Characteristics of study participants in whole group and MRI substudy

	All (n=5461)	MRI substudy (n=553)
Demographics		
Number of visits, mean (SD)	12.7 (2.4)	12.9 (1.5)
Age, years, mean (SD)	75.3 (3.3)	74.9 (3.2)
Female, n (%)	2822 (51.7)	241 (43.6)
Age left school, years, mean (SD)	15.1 (2.1)	15.5 (2.9)
Vascular risk factors		
History of hypertension, n (%)	3399 (62.2)	341 (63.1)
History of diabetes mellitus, n (%)	576 (10.5)	91 (16.5)
History of stroke or TIA, n (%)	606 (11.1)	89 (16.1)
History of myocardial infarction, n (%)	714 (13.1)	67 (12.1)
History of vascular disease, n (%)	2404 (44.0)	240 (43.4)
Current smoker, n (%)	1433 (26.2)	115 (20.8)
Body mass index , kg/m^2, mean (SD)	26.9 (4.2)	26.7 (3.6)
Total cholesterol, mmol/L, mean (SD)	5.7 (0.9)	5.7 (0.8)
Blood pressure, mean (SD)		
Systolic blood pressure, mm Hg*	153.1 (16.1)	156.1 (16.4)
Diastolic blood pressure, mm Hg *	82.5 (7.5)	85.1 (7.3)
Variability in systolic blood pressure, mm Hg**	14.8 (5.0)	13.9 (4.6)
Variability in diastolic blood pressure, mm Hg**	7.1 (2.9)	7.4 (2.3)
Cognitive function, mean (SD)* **		
Stroop test score, seconds	69.4 (31.6)	56.9 (23.3)
Letter-Digit Coding test score, digits coded	21.8 (8.0)	26.3 (7.4)
PLTi score, pictures remembered	9.2 (2.2)	10.1 (2.2)
PLTd score, pictures remembered	9.8 (3.1)	11.1 (3.0)
MRI features		
Grey matter, ml, mean (SD)	---	590 (44)
White matter, ml, mean (SD)	---	768 (38)
Hippocampus, ml, mean (SD)	---	7.5 (1.1)
Micro-bleeds, n (%)	---	124 (24.0)
Infarcts, n (%)	---	180 (33.6)
Cortical	---	65 (12.1)
Lacunar	---	112 (21.0)
WMH volume, ml, mean (SD)	---	7.2 (1.1)

Abbreviations: SD, standard deviation; n, number; TIA, transient ischemic attack; PLTi, Picture-Word Learning Test immediate; PLTd, Picture-Word Learning Test delayed; WMH, white matter hyperintensity. * defined as the mean of all blood pressure measurements during follow-up. ** defined as the standard deviation of all blood pressure measurements during follow-up. *** defined as the cognitive test score at the end of follow-up.

Table 3 shows the association of visit-to-visit variability in systolic and diastolic blood pressure with structural brain volumes. Higher variability was associated with lower hippocampal volume (both p-values=0.01). There was no association between blood pressure variability and volume of the other brain structures (all p-values>0.05), except for the association between higher variability in systolic blood pressure and lower amygdala and putamen volumes (both p-values=0.04). Analyses were adjusted for average systolic and diastolic blood pressures, which themselves were not associated with structural brain volumes (all p-values>0.05) (supplemental table 5).

Table 2. Cognitive function in thirds of visit-to-visit blood pressure variability

	Third of visit-to-visit blood pressure variability			
	Low (n=1820)	Middle (n=1821)	High (n=1820)	P-value
Systolic blood pressure				
Range of SD, mm Hg	0.7-12.2	12.3-16.2	16.3-64.4	
Stroop, seconds	68.46 (0.79)	68.75 (0.79)	71.54 (0.82)	<0.001
LDCT, digits coded	22.40 (0.19)	21.82 (0.19)	21.24 (0.19)	<0.001
PLTi, pictures remembered	9.37 (0.05)	9.28 (0.05)	9.10 (0.05)	<0.001
PLTd, pictures remembered	10.00 (0.07)	9.89 (0.07)	9.70 (0.08)	0.001
Diastolic blood pressure				
Range of SD, mm Hg	0-6.5	6.6-8.5	8.6-33.1	
Stroop, seconds	68.28 (0.79)	68.89 (0.79)	71.34 (0.80)	<0.001
LDCT, digits coded	22.35 (0.19)	21.93 (0.19)	21.27 (0.19)	<0.001
PLTi, pictures remembered	9.41 (0.05)	9.22 (0.05)	9.13 (0.05)	<0.001
PLTd, pictures remembered	10.01 (0.07)	9.88 (0.07)	9.74 (0.07)	0.001

Abbreviations: SD, standard deviation; n, number; LDCT, Letter-Digit Coding test; PLTi, Picture-Word Learning Test immediate; PLTd, Picture-Word Learning Test delayed. Data are adjusted values of the mean (standard error) of each cognitive function test. Adjustments were made for age, sex, body mass index, Statin treatment, apoE genotype, country, education, test version where appropriate, smoking, cholesterol levels, history of vascular diseases, history of hypertension, history of diabetes mellitus, and average blood pressure measures.

Table 3. Structural brain volumes in three groups of visit-to-visit blood pressure variability

	Three groups of visit-to-visit blood pressure variability			
	Low	Middle	High	P-value
Systolic blood pressure	(n=194)	(n=210)	(n=149)	
Range of SD, mm Hg	0.7-12.2	12.3-16.2	16.3-64.4	
Grey matter	593 (3)	590 (3)	589 (3)	0.21
White matter	770 (3)	770 (3)	765 (3)	0.19
Hippocampus	7.6 (0.07)	7.6 (0.07)	7.4 (0.08)	0.01
Diastolic blood pressure	(n=178)	(n=184)	(n=191)	
Range of SD, mm Hg	0-6.5	6.6-8.5	8.6-33.1	
Grey matter	591 (3)	594 (3)	587 (3)	0.18
White matter	768 (3)	772 (3)	764 (3)	0.62
Hippocampus	7.6 (0.07)	7.5 (0.07)	7.4 (0.07)	0.01

Data are structural brain volumes presented in mean (standard error) ml. Analyses were adjusted for age, sex, body mass index, Statin treatment, smoking, cholesterol level, history of vascular diseases, history of hypertension, history of diabetes mellitus, and average blood pressure measures.

Table 4 shows the association between visit-to-visit variability in blood pressure and cerebral microbleeds, infarcts, and white matter hyperintensities. Higher variability in systolic and diastolic blood pressure was associated with a higher risk of cortical infarcts (both p-values=0.02). Prevalence of cortical infarcts in participants with low, middle, and high variability in systolic blood pressure was 9.2%, 12.0%, and 16.2%, respectively. Prevalence of cortical infarcts in participants with low, middle, and high variability in diastolic blood pressure was 7.9%, 13.3%, and 16.2%, respectively. Furthermore, higher variability in diastolic blood pressure was associated with a higher risk of all types of microbleeds (p-value=0.01) as well as subcortical microbleeds (p-value=0.004). Prevalence of microbleeds in participants with low, middle, and high variability in systolic blood pressure was 21.2%, 23.9%, and 28.4%, respectively. Prevalence of cortical infarcts in participants with low, middle, and high variability in diastolic blood pressure was 17.8%, 27.5%, and 28.9%, respectively. Variability in systolic and diastolic blood pressure was not associated with white matter hyperintensities (both p-values>0.05). We found no association of average systolic and diastolic blood pressure with cerebral microbleeds, infarcts, and white matter hyperintensities (all p-values>0.05) (supplemental table 6).

Table 4. Microbleeds, infarcts and white matter hyperintensities in three groups of visit-to-visit blood pressure variability

	Three groups of visit-to-visit blood pressure variability			
	Low	Middle	High	P-value
Systolic blood pressure	(n=207)	(n=191)	(n=137)	
Range of SD, mm Hg	0.7-12.2	12.3-16.2	16.3-64.4	
Microbleeds, OR (95% CI)	1 (ref)	1.13 (0.69-1.85)	1.30 (0.77-2.21)	0.39
Infarcts, OR (95% CI)	1 (ref)	0.95 (0.61-1.48)	1.26 (0.78-2.04)	0.40
Cortical	1 (ref)	1.34 (0.68-2.64)	2.22 (1.09-4.54)	0.02
Lacunar	1 (ref)	0.79 (0.48-1.31)	0.84 (0.48-1.46)	0.97
WMH volume, ml, mean (SE)	8.12 (1.02)	7.34 (1.08)	7.79 (1.19)	0.98
Diastolic blood pressure	(n= 215)	(n= 166)	(n= 154)	
Range of SD, mm Hg	0-6.5	6.6-8.5	8.6-33.1	
Microbleeds, OR (95% CI)	1 (ref)	1.75 (1.05-2.91)	1.77 (1.06-2.96)	0.01
Infarcts, OR (95% CI)	1 (ref)	0.99 (0.63-1.56)	1.32 (0.84-2.06)	0.43
Cortical	1 (ref)	1.87 (0.93-3.76)	2.19 (1.10-4.37)	0.02
Lacunar	1 (ref)	0.95 (0.57-1.60)	1.17 (0.70-1.95)	0.75
WMH volume, ml, mean (SE)	7.65 (1.05)	8.27 (1.11)	7.93 (1.10)	0.55

Abbreviations: SD, standard deviation; n, number; OR, odds ratio; CI, confidence interval; WMH, white matter hyperintensity; SE, standard error. Analyses were adjusted for sex, age, body mass index, Statin treatment, smoking, cholesterol levels, history of vascular diseases, history of hypertension, history of diabetes mellitus, and average blood pressure measures. Data for microbleeds, infarcts and white matter hyperintensities were available for 535 participants.

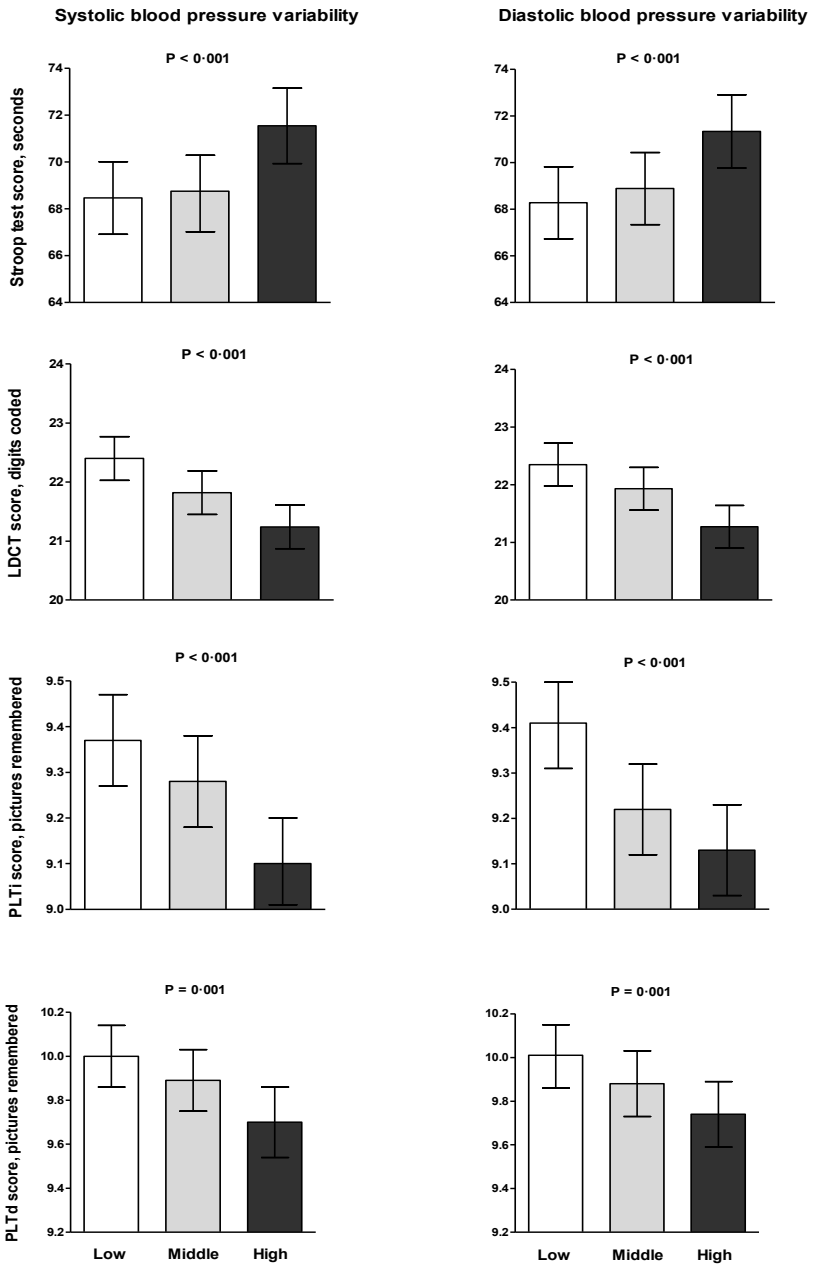

Figure 1. Cognitive function in thirds of visit-to-visit blood pressure variability
Stroop test, Letter-Digit Coding Test (LDCT), immediate Picture-Word Learning Test (PLTi) and delayed Picture-Word Learning Test (PLTd) scores in low, middle and high thirds of systolic and diastolic visit-to-visit blood pressure variability. Bars represent mean and 95% confidence interval. All analyses were adjusted for age, sex, body mass index, Statin treatment, apo E genotype, country, education, test version where appropriate, smoking, cholesterol level, history of vascular diseases, history of hypertension, history of diabetes mellitus, and average blood pressure measures

We performed four sensitivity analyses to explore whether the association of visit-to-visit variability in blood pressure with the studied outcomes could be affected by participants with a history of clinical stroke or transient ischemic attack (n=606) and cardiovascular disease (n=2404), participants with new or a change in antihypertensive therapy during the study period (n=2733), participants who developed vascular events (n=872) or arrhythmia (n=506) during the study period, and participants with a high average blood pressure (defined as average systolic blood pressure of ≥140 mm Hg and diastolic blood pressure of ≥80 mm Hg during the study period) (n=830). These sensitivity analyses showed that the results did not materially change. In an overall sensitivity analysis we excluded all participants with the aforementioned conditions (n=4654) and the results remained essentially unchanged (data not shown).

Discussion

Higher visit-to-visit variability in systolic and diastolic blood pressure was associated with worse performance in different domains of cognitive function and lower hippocampal volume and risk of cortical infarcts. Higher variability in diastolic blood pressure was associated with risk of cerebral microbleeds. These associations were independent of various cardiovascular risk factors, in particular average systolic and diastolic blood pressures.

Although hypertension is a well-established risk factor for cardiovascular diseases, increasing evidence indicates that the predictive value of conventional blood pressure measurement for cardiovascular diseases attenuates with increasing age.(22-24) Recent studies have shown that higher visit-to-visit variability in blood pressure increases the risk of cardiovascular events, stroke, and carotid artery atherosclerosis in older people, independent of average blood pressure.(1, 24-26) Given the link between neurovascular dysfunction and cognitive impairment, a recent study on 201 elderly participants (mean age 79.9 years) at high risk of cardiovascular disease showed that high visit-to-visit variability in blood pressure during 12 months was associated with worse performance in the mini-mental state examination and global deterioration scale.(27, 28) Consistent with this finding, by using a population of over 5000 participants and over three years of blood pressure measurements, we showed that high visit-to-visit variability in both systolic and diastolic blood pressure was associated with worse performance in different domains of cognitive function, including selective attention, processing speed, immediate verbal memory, and delayed verbal memory.

The magnitude of associations in this study, reflected as differences in cognitive scores between top and bottom thirds of variability in systolic and diastolic blood pressure, are comparable with the observed differences in cognitive function between groups of apolipoprotein E genotype on cognitive function.(29) The apolipoprotein E4 genotype is a well-recognized risk factor for the development of dementia in later life and it has been shown that people who carry this risk factor have a four times higher risk of developing late onset Alzheimer`s disease.(30) Similar differences in cognitive test scores in apolipoprotein E groups and variability in blood pressure implies that the observed associations can be considered clinically relevant.

Different explanations can be proposed for the observed association between high visit-to-visit variability in blood pressure and impaired cognitive function. Firstly, both blood pressure variability and cognitive impairment could stem from a common cause, without themselves being causally related. Cardiovascular risk factors are the most likely candidate.(31) Nevertheless, we reported our analyses adjusted for different cardiovascular risk factors and we performed a sensitivity analysis, by separately excluding those with a history of cardiovascular diseases. This did not change our estimates, although we accept that residual confounding could remain from unmeasured risk factors for cardiovascular disease. As a second explanation, high visit-to-visit variability in blood pressure might reflect a long term hemodynamic instability in the systemic circulation that puts stress on the vascular endothelium.(7, 32) This hemodynamic stress may lead to endothelial dysfunction and micro-vascular damage with consequent alterations in brain structure and function.(33) Thirdly, exaggerated fluctuations in systemic blood pressure could result in repeated episodes of cerebral hypoperfusion causing neuronal injury and cell death, particularly in vulnerable brain regions such as the hippocampus.(4) In line with latter explanations, we found that higher visit-to-visit variability in blood pressure is related to lower hippocampal volume and the presence of cerebral microbleeds and cortical infarcts. Given the well described association of hippocampal atrophy and cerebral small vessel disease with cognitive impairment, our findings may suggest that decreased hippocampal volume, cerebral microbleeds, and cortical infarcts are potential pathogenic mechanisms behind the association between variability in blood pressure and cognitive impairment.(10, 34)

Current evidence on the association of blood pressure variability with structural brain damage and cerebral small vessel disease mainly comes from studies that focused on ambulatory blood pressure rather than visit-to-visit variability. These studies showed that higher variability in ambulatory blood pressure is associated with brain atrophy and white

matter lesions.(35-37) In the present study, we only observed the association of visit-to-visit variability in blood pressure with lower hippocampal volume, cerebral microbleeds, and cortical infarcts. This might imply that different measures of blood pressure variability carry different predictive values for brain outcomes.(24) Data on the association between visit-to-visit variability and manifestations of small vessel diseases are scarce. Consistent with our findings, a recent study showed that higher visit-to-visit variability in blood pressure in people with a history of ischemic stroke was associated with progression of cerebral microbleeds but not with white matter lesions.(38) It is, however, still unclear whether higher variability in blood pressure is a cause or consequence of brain disease. It has been suggested that higher variability itself could originate from previously established brain diseases disturbing central autonomic control.(39) While clinical trials have shown conflicting findings on the benefit of antihypertensive therapy on reducing the risk of dementia, calcium channel blockers, the most effective drug class to reduce variability in blood pressure, showed significant efficacy in lowering the risk of vascular cognitive impairment.(40, 41) This might highlight potential clinical implications of agents reducing blood pressure variability in lowering the risk of brain vascular disease and cognitive impairment in old age. Collectively, we are not able to make a causal inference from our observation, and future long term investigations are warranted to examine whether strategies to reduce variability in blood pressure can effectively decrease the risk of cognitive impairment as well as of brain vascular disease.

The major strengths of this study include a large sample size and application of an extended standardized cognitive test battery to assess cognitive function. In addition, availability of neuroimaging data provided us with a unique opportunity to investigate potential biological pathways linked to the association between variability in blood pressure and cognitive function. However, this study has certain limitations. Firstly, we included elderly participants at risk of cardiovascular diseases with relatively preserved cognitive function (mini-mental state examination $\geq$24 points), which might limit the extrapolation of our findings to a general elderly population. However, this restriction has possibly resulted in a homogeneous study population who are among the main target groups for preventing cognitive decline.(42) Secondly, the outcomes of this study were evaluated at one time point, and long term longitudinal studies are needed to test whether lowering variability in blood pressure could lead to decelerated cognitive decline and lower the burden of brain diseases. Thirdly, owing to the limited number of participants in the magnetic resonance imaging substudy, we had limited power in several outcome measures. This means that the absence of significant associations for several outcome measures should be interpreted

with caution. There are reports indicating that higher visit-to-visit variability in blood pressure is related to a higher risk of stroke and cerebrovascular damage, however, the exact mechanisms behind these associations are still unclear.(1) This problem needs to be addressed in future magnetic resonance imaging studies with larger number of participants. Fourthly, although we adjusted our analyses for different potential confounding factors, some other confounders may exist that we did not consider in our analyses. Future studies investigating the determinants of visit-to-visit variability in blood pressure might help to understand better the association between variability in blood pressure and neurocognitive outcomes.

In conclusion, our findings suggest that higher visit-to-visit variability in blood pressure independent of average blood pressure is associated with worse cognitive performance in older people at high risk of cardiovascular disease. Changes in hippocampal volume and occurrence of cortical infarcts and cerebral microbleeds might be candidate pathogenic mechanisms behind this association. This observation merits further interventional studies to determine whether reducing variability in blood pressure can decrease the risk of cognitive impairment in old age.

References

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