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Cross-sectional associations between short and mid-term blood pressure variability, cognition, and vascular stiffness in older adults

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ABSTRACT

Background: High blood pressure variability (BPV), particularly in older age, appears to be an independent risk factor for incident dementia. The current study aimed to investigate the association between different BPV measures (short- and mid-term BPV including circadian patterns) and cognitive functioning as well as vascular stiffness measures to better understand the role that BPV plays in cognitive impairment.
Methods: 70 older adults (60–80-year-olds) without dementia completed a cognitive test battery and had their blood pressure (BP) assessed via a 24-hour ambulatory BP monitor (divided into sleep and wake for short-term BPV) and 4-day morning and evening home-based BP monitor (for day-to-day BPV). Arterial stiffness was evaluated via pulse wave analysis and pulse wave velocity (PWV) and cerebrovascular pulsatility was assessed via transcranial doppler sonography of the middle cerebral arteries.
Results: High systolic as well as diastolic short- and mid-term BPV were associated with poorer cognitive functioning, independent of the mean BP. Higher short-term BPV was associated with poorer attention and psychomotor speed, whilst day-to-day BPV was negatively linked with executive functioning. Circadian BP patterns (dipping and morning BP surge) showed no significant relationships with cognition after adjusting for covariates. Higher systolic short-term BPV was associated with higher arterial stiffness (PWV) and higher diastolic day-to-day BPV was linked with lower arterial stiffness. No significant associations between BPV measures and cerebrovascular pulsatility were present.
Conclusion: High BPV, independently of the mean BP, is associated with lower cognitive performance and increased arterial stiffness in older adults without clinically-relevant cognitive impairment. This highlights the role of systolic and diastolic BPV as a potential early clinical marker for cognitive impairment.

1. INTRODUCTION

High blood pressure (BP), particularly in midlife, is a well-known cardiovascular risk factor for cognitive decline and dementia [1]. Whilst research relating to BP has usually focused on hypertension and mean BP, the clinical relevance of the fluctuating nature of BP has recently been identified [2,3]. BP variability (BPV) has been recognized as an important predictor for adverse cardiovascular outcomes (e.g. stroke, myocardial infarction) and mortality, independent of the mean BP [4,5]. High BPV has also been linked with adverse structural brain changes, including lower hippocampal volume and increased white matter hyperintensities [6,7]. Two recent meta-analyses [8,9] have also shown that increased BPV, particularly in older age, is linked with a higher risk of developing dementia. Notably, the association between BPV and cognitive impairment appears stronger than that for mean BP [9].

The majority of studies so far have focused on (i) long-term BPV and (ii) cognitive impairment (e.g. mild cognitive impairment or dementia), whilst investigations between short-term (across 24 hours) and mid-term BPV (across days), and cognitive functioning are scarce and conflicting [2,10]. Short-term BPV can provide insight into the circadian patterns of BP, including the nocturnal BP fall and the morning BP surge [3,11]. During sleep, systolic and diastolic BP usually show a decline of 10-20%, which is referred to as 'dipping' [11,12]. Individuals can also

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show abnormal nocturnal BP changes which can be classified into the following three groups: 'extreme-dippers' (>20%), 'non-dippers' (<10%), and 'reverse-dippers' (who show an increase instead of a decrease in nocturnal BP) [11,13]. Whilst abnormal night-time BP patterns, as well as an exaggerated increase in the morning BP surge, have been linked with an increased risk of cardiovascular events [14–17], the relationship between circadian BPV patterns and cognition is not well understood.

One important factor to consider when exploring the link between BPV and cognitive function is arterial stiffness. Arterial stiffness, reflected by reduced arterial elasticity and compliance, increases with age and can be measured by parameters like the pulse wave velocity (PWV) and the augmentation index (AIx) [18]. Arterial stiffness is a well-established cardiovascular risk factor for cognitive impairment and has a strong bidirectional relationship with hypertension [19,20]. The link between arterial stiffness and cognitive decline is likely mediated by cerebral vascular functioning, including cerebral pulsatility [21,22]. There is evidence that changes in vascular functioning, such as a decline in cerebral blood flow occur before structural neuroanatomical changes (e.g. hippocampal atrophy) [21,23]. Increased systolic short-term BPV, has recently been linked with higher arterial stiffness in hypertensive patients [24–26]. Abnormal circadian BP patterns, including an exaggerated morning BP surge, have been independently linked with increased arterial stiffness in hypertensive individuals [27]. Multiple studies have reported that non-dippers show significantly higher arterial stiffness (assessed via PWV) than dippers [28–30]. However, the relationship between short-term BPV and arterial stiffness outside of a hypertensive sample is unclear. Further, there is a lack of studies that have investigated mid-term BPV and arterial stiffness.

The link between BPV and cerebrovascular pulsatility remains poorly understood [31]. High BPV has been linked with cerebral small vessel disease [7,32], which is associated with increased cerebral vessel pulsatility [33]. Transcranial Doppler sonography (TCD) is a non-invasive assessment tool that provides great utility in assessing cerebral vessel integrity including cerebrovascular pulsatility, due to its high temporal resolution [34]. The current study will use TCD to assess pulsatility of the middle cerebral artery as a measurement of cerebrovascular stiffness and measure arterial stiffness through PWV and brachial pulse wave analysis (AIx) in a sample of community dwelling older adults. An improved understanding of the relationship between BPV and arterial stiffness as well as cerebral pulsatility, may help to better understand the mechanistic link between increased BPV and cognitive impairment.

The heterogeneity in BPV metrics and assessments, due to a lack of consensus, make it particularly challenging to understand the link between short-term BPV, cognition, and arterial stiffness, as not all measures sufficiently account for day/night variations [2]. Studies have usually looked at short-term BPV, circadian patterns and mid-term BPV in isolation, which makes it difficult to understand whether they show similar or different associations with cognitive functioning and vascular stiffness. The current study used a comprehensive assessment to investigate BPV by measuring short-term, circadian and mid-term BPV through three different BPV metrics. Looking at short-term, circadian, and day-to-day BPV in relation to cognitive functioning and vascular health will improve our understanding of BPV as a potential clinical marker and modifiable vascular risk factor for dementia. We hypothesise that high short-term BPV, higher mid-term BPV, and abnormal circadian BP patterns are linked with (i) reduced cognitive functioning, (ii) increased arterial stiffness, and (iii) increased cerebrovascular pulsatility, independent of the mean BP.

2. METHODS

This study is a cross-sectional quantitative observational study.

2.1. Participants

Between March 2020 and April 2022, participants with and without BP problems were recruited through the distribution of recruitment posters to community groups and places across Adelaide (SA, Australia). Participants were recruited if they were aged 60 to 80 years and proficient English speakers. Exclusion criteria were: a history of psychiatric or neurological disorders, a history of ischaemic or valvular heart disease; cardiac arrhythmias; cerebrovascular accidents; traumatic brain injury; renal failure; stroke; respiratory problems (i.e. asthma, sleep apnoea), irremovable hearing aids, history of alcoholism or other substance abuse disorders within the past 10 years, current smokers, diagnosed sleep and or circadian rhythm disorder, current shift work, trans meridian travel within the past 2 weeks, diagnosis of clinical dementia, change in antihypertensive medication within the past 6 months, any symptoms of COVID-19 at the time of testing, or exposure to suspected or diagnosed COVID-19 patients. Of the 71 recruited participants, one did not complete the testing due to a COVID-19 lockdown, leading to a total sample of 70 participants. Day-to-day BPV data were available for 69 participants and ambulatory BP data of 65 individuals. For 17 of the 70 participants, no TCD signal of sufficient quality could be recorded. This study was approved by the Human Research Ethics Committees of the University of South Australia and all participants gave their informed consent prior to their inclusion in the study.

2.2. Procedure

Prior to the first visit, all participants completed a phone screening, where eligibility was assessed. Testing was conducted across a week, including 3 in-person study visits that took place at the University of South Australia (see Fig. 1). Demographic measures collected at the first visit included: age, gender, years of education, antihypertensive treatment status, weight, height, diabetes, and smoking history of the participants. Participants received verbal as well as written instructions during the study visits on how ambulatory and at home BP should be measured. All physiological measures (TCD and central BP measures) were conducted by the same researcher. Participants were asked to fill out a sleep diary for the duration of the study, where they recorded the time they went to bed (lights out) and the time they woke up. Participants also wore a tri-axial accelerometer (GENEActiv: Activinsights Ltd, Cambridgeshire, United Kingdom) on the wrist of the non-dominant arm for the duration of the study.

2.3. Cognitive Assessment

Cognition was assessed during Visit 1 through the Modified Mini-Mental State (3MS)[35] examination and through subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (CANTAB® Cambridge Cognition 2019).

2.3.1. 3MS

The 3MS [35] English version, was used as an assessment tool for global cognitive performance. The 3MS consists of 15 items that make up a total score range of 0 to 100, with higher scores indicating better performance. Studies have found a high test-retest-reliability for the 3MS in older persons [36] and reported a high sensitivity in the identification of cognitive impairment and mild dementia with a cut-off score of 78 [37], which was used in the current study. The 3MS has also previously been used in cardiovascular health studies and has been found to be sensitive in detecting cognitive changes in relation to hypertension in older adults [36].

2.3.2. CANTAB

Six CANTAB subtests, administered via an iPad, were included to further assess cognitive functioning. CANTAB is a widely used neuropsychological test battery, that has been found to be a sensitive tool to

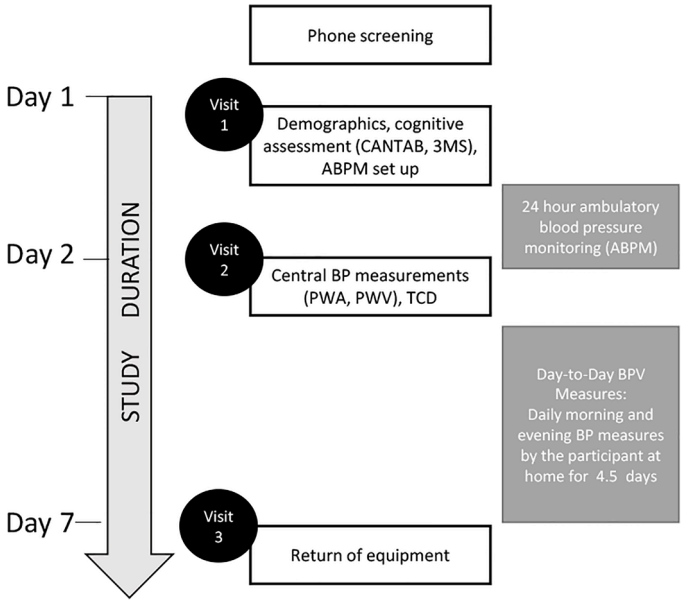

Fig. 1. Study procedure by visits.
ABPM Ambulatory blood pressure monitor, *BP* Blood pressure, *BPV* Blood pressure variability, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *TCD* Transcranial doppler sonography, *PWA* Pulse wave analysis, *PWV* Pulse wave velocity, *3MS* Modified Mini-Mental State examination.

measure different cognitive domains in clinical and non-clinical populations. The CANTAB subtests that were selected for this study were presented in the following order (1) Motor Screening Task, (2) Reaction Time, (3) Rapid Visual Information Processing, (4) Paired Associate Learning, (5) Multitasking Test and (6) Spatial Working Memory test. The Motor Screening Task was used to familiarise test subjects with the touch screen of the computer and was not included as a cognitive outcome measurement. The selected tests focus on the cognitive domains of memory, executive functioning, and psychomotor speed (see Supplementary Table S1), and have been found to be sensitive in detecting cognitive impairment in cerebrovascular disease [38]. For each subtest, the recommended key variables from CANTAB were extracted to measure performance, as outlined in Table S1.

2.4. Vascular stiffness

2.4.1. Cerebrovascular pulsatility - Trans cranial doppler sonography

The Qi 2.8 software with the DWL 12 Doppler-Box hardware (Compumedics, DWL, Singen, Germany), with two ultrasonic probes (sampling rate 2MHz), was used to record the blood flow velocities of the middle cerebral arteries through the trans-temporal windows at 100 Hz for 65 seconds each during eyes open and eyes closed. The first and last 2.5 seconds of the recording were removed. Participants were in a sitting position during set-up and recording. Unilateral or averaged bilateral TCD data (depending on signal availability) was used to calculate the systolic/maximum, diastolic/ minimum, and mean, blood flow velocity as well as the pulsatility index ((systolic velocity– diastolic velocity) / mean velocity) [39]. The pulsatility index provides information about the diastolic cerebrovascular resistance and is understood to be a measurement of cerebral arterial stiffness [40].

As there was no difference in the patterns of association between eyes open and eyes closed TCD measures, the average of eyes open and eyes closed data were used for analyses.

2.4.2. Arterial stiffness

Arterial stiffness was noninvasively measured through pulse wave analysis and through PWV (SphygmoCor XCEL; AtCor Medical, West Ryde, Australia).

2.4.2.1. Pulse wave analysis. The central aortic pressure waveform was measured through cuff-based volumetric displacement from the brachial artery on the left arm of participants, in a sitting position with forearms supported. SpgygmoCor XCEL applies a general transfer function to the peripheral acquired signal to compute the aortic waveform. A derived measurement from the waveform analysis is the AIx. The AIx is calculated as the augmentation pressure (systolic central pressure – inflection pressure) divided by the pulse pressure (systolic – diastolic pressure) and is normalised to a heart rate of 75 bpm [41]. The augmentation index is affected by the magnitude and timing of the reflected waveform and is hence influenced by the structure and compliance of the vessel. A higher augmentation index is reflective of increased arterial stiffness [41].

2.4.2.2. Pulse wave velocity. Carotid-femoral PWV was assessed through a simultaneous measure of the carotid pulse via a tonometer and the femoral pulse via a cuff fitted around the right thigh. The PWV was derived from the foot-to-foot pulse time difference between the two measurement sides, relative to the distance between them, as identified from predefined measurement points (see Butlin & Quasem [41] for a detailed outline of the measurement sides and calculation). A higher PWV measurement is reflective of increased arterial stiffness.

2.5. Blood pressure variability

2.5.1. Short-term blood pressure variability

Short-term BPV was measured with a 24-hour oscillometric ambulatory BP monitor (A&D Medical, Model TM-2440). At the end of the first study visit, an appropriately sized BP cuff, that was connected to the BP monitor, was fitted around the left arm of the participants. BP measurements were taken every 15 min throughout the day (7:00 – 22:00) and every 30 min through the night (22:00 – 7:00). Participants were instructed to follow their usual daily routines, including sleep, during the 24- hour period, but to avoid vigorous physical activity and to keep the left arm still and relaxed for each measurement. The reading and quality assessment of the AMBP readings were done through the ABPM Data Analysis Software from A&D Medical (version 1.1.3; A&D Instruments, Abingdon, UK). The first BP reading was excluded for all participants. A minimum of 50% of valid BP readings needed to be present for the day (minimum of 30 readings) and for the night

(minimum of 9 readings) for the measurement to be included.

The ambulatory BP data was subdivided into day and night (day 7:00-22:00, night 22:00-7:00) as well as into wake and sleep (based on individual sleep diaries) for subsequent analyses. A minimum of nine valid BP readings were necessary for the sleep-duration to be included. The circadian BP patterns were assessed via the systolic BP dipping proportion (dip proportion = 1 – mean sleep systolic BP/mean wake systolic BP) and the morning BP surge. The morning BP surge was assessed as pre-awakening systolic BP surge, as outlined in Kario et al. [42], where the average pre-awakening systolic BP (two hours before wake) is subtracted from the post-awakening systolic BP (2 hours post wake), based on the sleep diary. A minimum of three valid BP readings each in the pre-awakening and in the post-awakening time were required.

2.5.2. Day-to-Day blood pressure variability

For the day-to-day BP recordings home-based BP measurements were taken by the participant using a validated, memory-equipped, automatic oscillometric device (A&D Medical, Model UA-651SL). At the end of the second study visit participants received spoken and written instructions on how to conduct the home-based BP measurements and 3 practice measurements, under the supervision of the researcher, were taken. Participants were instructed to measure their own BP at home for the next 4.5 days in the mornings (within 1 hour of awakening, before breakfast) and at night (1 hour before going to bed and minimum one hour after dinner). For each BP assessment, 3 individual BP readings had to be taken, 1 minute apart, in a seated position and after 5 minutes of rest (see supplement Table S2 for the written instructions participants received). The readings from the laboratory and the first home-based night BP measurement (including 3 readings) were discarded for the analysis. The average of the 3 individual readings was taken for the subsequent day-to-day variability analysis. A minimum of 3 day and 3-night readings were required for the measurement to be included in the analysis. For participants that forgot to take a reading but took an additional reading on the last study day, the additional reading was included in the analysis (n=2). Day-to-day BPV, was computed separately for morning and evening readings.

2.5.3. Blood pressure variability metric

All BP data was analysed through the '*BP*' package [43] in R (RStudio Team, 2020). BPV is usually analysed as the degree of dispersion, which can be calculated in different ways [12,44]. Whilst the standard deviation is a commonly used measurement, its appropriateness as an index of BPV has been questioned, as it only reflects the dispersion of values around the mean, and is sensitive to low sampling frequencies [44–46]. A measurement that has gained substantial support in BPV [47], is the ARV, which computes the average absolute variation between consecutive BP readings [44]

$$ARV = \frac{1}{N-1}\sum_{k=1}^{N-1}|BP_{k+1} - BP_k|$$

N denotes the number of BP measurements, and k represents the order of the measurements. Considering the fluctuations between readings is of particular interest for the assessment of short-term BPV, as it is less affected by circadian changes [3,13]. In addition, across multiple studies ARV has been found to be a stronger predictor, for cardiovascular risk than other BPV indices [46–49]. The current study used ARV as the primary measurement of BPV for short as well as mid-term BPV. As it is currently still unclear whether different metrics have separate clinical implications, in line with the suggestion by Levitan et al. [47] we also included two additional measures of variability for the initial assessment. The coefficient of variation (CV) (CV = 100 x SD/$\bar{x}_i$), is a metric of overall variability that controls for the mean, and the range that focuses on extreme values [47]. For the assessment of day-to-day BPV the BP mean for each morning (day 3 to day 6) and evening (day 3 to day 6) measure was used to calculate the variability between morning day-to-day BPV and evening day-to-day BPV.

2.6. Statistical analysis

Statistical analysis was conducted through R.4.1.0 (RStudio Team, 2020).

Data was screened for normality via the Shapiro-Wilk test. BP readings that had a systolic >240/<50 mm HG or diastolic >140/<40 mm HG pressure were excluded. For the CANTAB data extreme outliers in key variables (identified through boxplots) were removed for that subtest for subsequent analysis. This led to the removal of 2 outliers in the Rapid Visual Information Processing task and 1 outlier in the Multitasking Test.

2.6.1. Association between BPV, cognition and vascular stiffness

To identify cognitive outcome variables that are potentially associated with BPV, Spearman correlations were computed between systolic and diastolic BPV (non-parametric) (measures as ARV, CV and range), for short-term BPV and day-to-day BPV, and each CANTAB key outcome (13 measures) and overall 3MS score. Additional Spearman correlations were run to assess the correlations between systolic and diastolic BPV and central arterial stiffness (PWV and AIx) and cerebrovascular stiffness. The same was done for mean systolic and diastolic BP. There was no correction for multiple comparisons for correlations due to the exploratory nature of the research aims.

Cognitive and arterial health variables that had a significant Spearman correlation ($p<0.05$) with systolic or diastolic BPV (ARV) were included as outcome variables for subsequent separate multiple linear regressions, across Models 1-3. Participants that had a standard residual ≥3 in the linear regression model were excluded from the analysis. Model 1 was unadjusted and only included the identified BPV measurement as predictor. Model 2 was adjusted for age and mean BP (diastolic or systolic mean BP were used depending on whether the predictor was systolic or diastolic BPV). Model 3 for the cognitive outcomes additionally adjusted for gender, BMI, antihypertensive treatment status and years of education. Model 3 for the arterial health outcomes additionally adjusted for age, gender, BMI and antihypertensive treatment status. To adjust for multiple comparisons, a Bonferroni correction was applied. Different alpha levels were calculated based on the number of cognitive outcomes that measure the same cognitive domain across short-term or day-to-day BPV or by the number of vascular stiffness measures included for the linear regressions, leading to alpha levels ranging between 0.016 and 0.05. For clarity reasons the most conservative alpha value of 0.016 was applied across all linear regression models.

Due to a limited sample size, additional covariates for Model 3 were identified by running correlations (Pearson or Spearman depending on whether the variables were normally distributed or not) between the included outcome variables and demographic information (years of education, antihypertensive treatment status, BMI, diabetes, smoking history, gender) (not reported here). Demographic variables that were found to correlate with any of the cognitive outcomes were included as covariates in Model 3. The same applied for demographic variables that correlated with included vascular stiffness measures.

3. RESULTS

3.1. Participant characteristics

The demographic characteristics of the participants (n=70) are shown in Table 1. None of the participants fell into the cognitive impairment range, based on the total 3MS score (>78). Table 2 displays the descriptive statistics of the cognitive test performance, the BP data (including mean BP and BPV values) and the vascular stiffness examination data (including the TCD, PWV and pluse wave analysis data. The

Table 1
Demographic characteristics of participants (n=70).

Demographic characteristics	
Gender, n (%)	
Female	46 (66)
Male	24 (34)
Age in years, Median (range)	70 (60 -79)
BMI, Median (range)	26 (19 – 46)
Education in years, Mean (SD)	16 (3)
Past smoking status	
Former, n (%)	24 (35)
Never, n (%)	45 (65)
History of hypertension, n (%)	32 (46)
Antihypertensive treatment, n (%)	26 (37)
Diabetes, n (%)	6 (9)

mean short-term (24-hour) as well as the mean day-to-day BP level averaged across participants falls into a normal category (non-hypertensive) (see Table 2). Of the 60 participants that had night-time dipping data available, 36 (60%) fell into a normal category, 9 (15%) were classified as extreme dippers, 13 (22%) as non-dippers, and 2 (3%) as reverse dippers. Supplement Figure S1 illustrates the frequency of BP readings by hypertension grade for the ambulatory BP and home BP data from the 'bp' package. Supplementary Table S3 contains the descriptive statistics of the CV ad Range assessment for BPV.

Whilst short-term BP data was split into day (7:00- 22:00) and night (22:00-7:00), as well as into wake and sleep (based on sleep diaries), the correlational analyses showed that day/night and wake/sleep BPV showed similar patterns of associations but stronger effect sizes for wake/sleep with cognitive and vascular measures (see supplement Table S3, Figure S2 and Figure S3 for day/night BP data). Hence subsequent analyses are based on the wake/sleep classification for short-term BPV. The blood pressure variability metrics (ARV, CV and BP range) were highly correlated across all BPV types (see supplement Tables S4-S7)

3.2. Associations between blood pressure variability and cognition

Fig. 2 illustrates the results of the Spearman correlations between short-term and day-to-day BP measures (BPV and mean BP) and cognitive measures. There were similar patterns of associations between the 3 BPV metrics (ARV, CV, range) and cognitive as well as vascular stiffness measures (see Fig. 2). However, for systolic short-term awake BPV and morning day-to-day BPV the effect sizes were stronger for ARV, with more correlations reaching a statistical significance (<0.05) for the ARV metric than for the CV or range variability metric. Mean BP and gender showed no significant associations with cognitive or vascular stiffness outcome measures across the linear regression models.

3.2.1. Short-term blood pressure variability

3.2.1.1. Awake short-term BPV. Higher systolic BPV (assessed via ARV) was significantly ($p<0.05$) correlated with lower cognitive performance across 8 CANTAB outcome measures, and overall cognition assessed via the 3MS, with medium to strong effect sizes. Each CANTAB task, apart from the Reaction Time Task, showed significant correlations with systolic BPV. Of the 9 identified cognitive outcome measures, 2 remained significantly associated with awake systolic BPV (ARV) across Model 1-3 that adjusted for age, mean BP and other covariates (Table 3 and Table S9). Higher systolic BPV was a significant predictor for reduced performance in the Rapid Visual Information Processing task (sustained attention) ($p=0.002$, $\beta = -0.42$) and a lower 3MS score ($p = 0.001$, $\beta = -0.41$). No significant correlations, and all with small to negligible effect sizes, were present between awake diastolic BPV (assessed vias ARV) and any cognitive measures. There were no significant correlations, with negligible effect sizes, between morning BP surge and cognitive measures.

Table 2
Descriptive statistics of cognitive test performance, blood pressure and vascular stiffness data

	N	Mean/ Median	SD/ Range
Cognitive test performance	70		
Modified Mini-Mental State (3MS) Examination			
Total score, Median (range)		96	80-99
CANTAB			
Motor screening task (MOT)			
Mean latency (in ms), Median (range)		864	593-1910
Reaction time (RT)			
Median reaction time (in ms), Mean (SD)		426	40
Median movement time (in ms), Median (range)		305	188 – 539
Rapid visual information processing (RVP)			
Target sequence sensitivity, Median (range)		1	0.8 – 1.0
Median response latency (in ms), Median (range)		494	394-944
Probability of false alarm, Median (range)		0.004	0.00-0.027
Paired associate learning (PAL)			
Total errors, Median (range)		19	2 -61
First attempt memory score, Median (range)		11	0 -18
Multitasking test (MTT)			
Median incongruency cost, Mean (SD)		108	11-318
Median reaction latency (in ms), Mean (SD)		787	102
Median multitasking cost, Mean (SD)		327	155
Total incorrect, Median (range)		5	0-35
Spatial working memory (SWM)			
Between errors, Median (range)		17	0 -31
Strategy, Median (range)		9	2 – 13
Blood pressure Data			
Short-term awake BP	62		
Mean systolic BP, Mean (SD)		131	13.8
Mean diastolic BP, Mean (SD)		78.8	8.2
ARV SBP, Median (range)		9.58	5.46-19.3
ARV DBP, Median (range)		7.4	4.1-12.4
Short-term sleep BP	65		
Mean systolic BP, Mean (SD)		114	16.7
Mean diastolic BP, Mean (SD)		67.5	9.0
ARV SBP, Median (range)		9.82	4.0-19.8
ARV DBP, Median (range)		6.5	2.9-19.1
Circadian BP Data	55		
Morning BP Surge, Mean (SD)		15.9	13.1
Day-to-Day Morning	69		
Mean systolic BP, Mean (SD)		127	16.0
Mean diastolic BP, Mean (SD)		75.6	8.7
ARV SBP, Median (range)		7.11	1.2-22.8
ARV DBP, Median (range))		4.22	0.2-16.1
Day-to-Day Evening	69		
Mean systolic BP, Mean (SD)		122	13.8
Mean diastolic BP, Mean (SD)		70.9	6.9
ARV SBP, Median (range)		8.56	1.0-37.0
ARV DBP, Median (range)		5.22	0.8-27.0
Transcranial doppler sonography Data	53		
Mean flow velocity [cm/s], Mean (SD)		38.4	11.1
Systolic velocity [cm/s], Mean (SD)		61.9	16.7
Diastolic velocity [cm/s], Mean (SD)		22.4	8.18
Pulsatility index (PI), Median (Range)		0.98	0.7-1.7
Pulse wave analysis	69		
Central Heart rate [bpm]		65.2	9.9
Central systolic [mmHG]		119	13.6
Central diastolic [mmHG]		75.9	7.7
Central Augumentation index (Aix) (%)		24.1	10.4
Carotid-femoral PWV [m/sec]	**58**	**8.9**	**1.7**

Note. Mean and standard deviation (SD) reported for parametric data and median and range reported for non-parametric data. *BP* blood pressure, *SBP* systolic BP, *DBP* diastolic BP, *BPV* blood pressure variability, *Mdn* median, *ARV* average real variability, *CV* coefficient of variation, *SD* standard deviation.

3.2.1.2. Sleep short-term BPV. There were no significant correlations ($p<0.05$), and all with negligible effect sizes, between sleep systolic BPV (assessed via ARV) and cognitive measures. One significant positive correlation, with a small to medium effect size, between sleep diastolic BPV and cognition (reaction time task) was present. This association

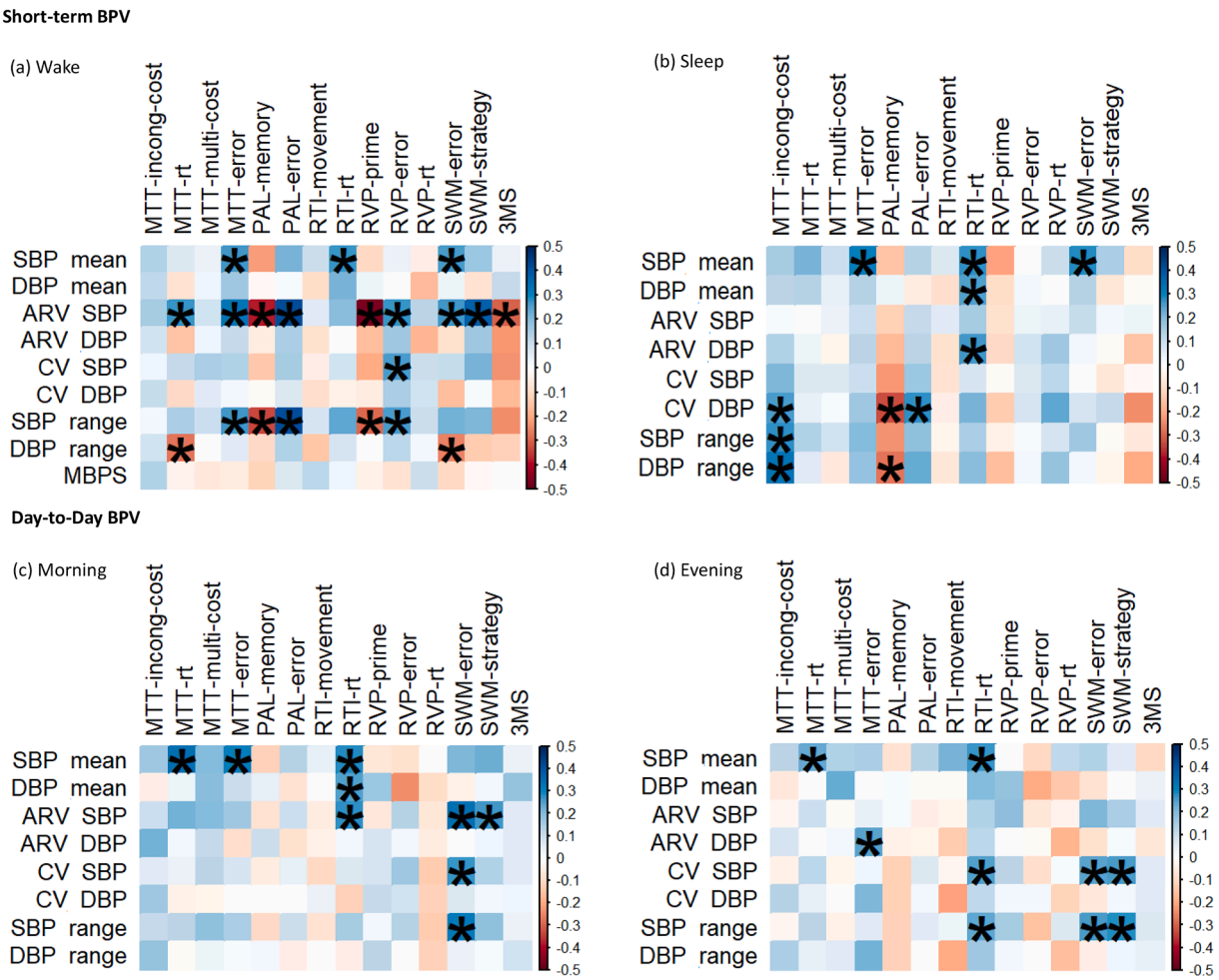

Fig. 2. Spearman correlations between blood pressure variability (BPV) measures and cognitive measures, with the colour indicating the correlation coefficient r. * Indicates significant correlations (p<0.05). ARV Average real variability, CV Coefficient of variation, SBP systolic blood pressure, DBP diastolic blood pressure, MTT Multitasking test, PAL Paired associate learning, RTI Reaction time task, rt reaction time, RVP Rapid visual information processing, SWM Spatial working memory.

remained significant (p<0.013) across linear regression Models 1 and 2 (p= 0.012, β = 0.32) but did not pass the adjusted alpha level in Model 3 (p = 0.029, β = 0.29) (see Table 3 and Table S9). There was one significant positive association between the dipping categories (with normal dipping as the reference point) and cognitive measures (reaction latency in the multitasking test) (see supplement Table S8). However, this association was no longer significant after controlling for covariates (Table 3).

3.2.2. Day-to-day blood pressure variability

3.2.2.1. Morning day-to-day BPV. Morning systolic BPV (assessed via ARV) was significantly (p<0.05) positively correlated, medium effect sizes, with 3 CANTAB outcome measures, 1 from the Reaction Time Task and 2 from the Spatial Working Memory Task. The between error score of the Spatial Working memory task stayed significantly negatively associated with Morning BPV in Model 1 and 2 (p= 0.010, β = 0.32), whilst the other 2 identified cognitive outcome measures did not (p > 0.013). No statistically significant correlations were present between diastolic BPV (for all three metrics) and cognitive measures, with small to negligible effects sizes.

3.2.2.2. Evening day-to-day BPV. None of the correlations between evening systolic BPV (ARV) and cognitive measures reached a statistically significant level (p<0.05). Small to medium effect sizes were present between evening systolic BPV (assessed via ARV) and the Spatial Working Memory outcomes (Fig. 2). There was one significant positive correlation between evening diastolic BPV (ARV) and the incongruency cost from the Multitask Test, with a medium effect size, but this association was no longer significant across the linear regression models (Table 3).

3.3. Associations between BPV and Vascular Stiffness

3.3.1. Short-term blood pressure variability

3.3.1.1. Awake short-term BPV. None of the Spearman correlations between systolic or diastolic BPV, or morning BP surge, and the vascular stiffness measures were statistically significant but there were small to medium effect sizes present (Fig. 3).

3.3.1.2. Sleep short-term BPV. Sleep systolic BPV was significantly positively correlated with PWV and the association stayed significant in Model 3 (p = 0.012, β = 0.30). Extreme dippers had a lower pulsatility index compared to dippers but just failed to reach statistical significance with the adjusted alpha value in Model 2 and 3 (p= 0.018) (see supplement Table S8 for non-significant associations with dipping patterns). Reverse dippers were correlated with higher PWV, but the association failed to reach statistical significance across the linear regression models (Table 4 and Table S10).

Table 3
Results of linear regression models for the association between BPV measures and cognitive measures with covariates

			Model 1			Model 2			Model 3		
Outcome	Predictor	N	β	CI [95%]	p	β	CI [95%]	p	β	CI [95%]	p
Short-term BPV - awake											
MTT– Reaction latency	ARV SBP	61	0.25	-0.01, 19.79	0.050	0.16	-3.73, 16.64	0.210	0.12	-5.74, 15.07	0.373
(Executive function)	Mean SBP		-	-	–	< 0.01	-1.86, 1.88	0.991	0.05	-1.61, 2.28	0.730
MTT– Total incorrect	ARV SBP	61 – 5 (res	0.26	0.00, 0.90	0.049	0.15	-0.19, 0.70	0.258	0.09	-0.31, 0.61	0.505
(Executive function)	Mean SBP	>3)		–	-	0.08	-0.06, 0.11	0.553-	0.15	-0.04, 0.13	0.179
					-	-	-				
PAL– Memory score	ARV SBP	62	-0.29	-0.95, -0.07	0.024	-0.20	-0.84, 0.14	0.153	-0.19	-0.87, 0.17	0.189
(Visual memory)	Mean SBP		–	-	–	-0.08	-0.11, 0.06-	0.563-	-0.09	-0.12, 0.07	0.538
PAL– Total errors	ARV SBP	62	0.26	0.09, 3.46	0.040-	0.17	-0.67, 3.02	0.207	0.18	-0.70, 3.16	0.206
(Visual memory)	Mean SBP					0.05-	-0.27, 0.40	0.687	0.07	-0.26, 0.45	0.586
RVP – A prime [#]	ARV SBP	60	-0.46	-1.33, -0.43	**<0.001**	-0.43 0.06	-1.33, -0.36	**0.001**	-0.42	-1.33, -0.31	**0.002**
(Sustained attention)	Mean SBP						-0.07, 0.11	0.628	0.04	-0.05, 0.11	0.741
RVP–False Alarm [#]	ARV SBP,	60- 2	0.20	-0.01, 0.07	0.136	0.21	-0.01, 0.07	0.170	0.14	-0.02, 0.06	0.350
(Sustained attention)	Mean SBP	(Res>3)	-	-	–	-0.07 -	-0.01, 0.01	0.635-	0.02	-0.01, 0.01	0.875
SWM –Error score	ARV SBP	62	0.20	-0.16, 1.38	0.118	0.04	-0.72, 0.94	0.790	0.03	-0.77, 0.98	0.814
(Working memory)	Mean SBP		–	–	–	0.24-	-0.02, 0.28-	0.082-	0.26	-0.02, 0.31	0.076
SWM –Strategy	ARV SBP	62	0.31	0.07, 0.58	0.013	0.22	-0.05, 0.50	0.105	0.22	-0.06, 0.52	0.123
(Executive function)	Mean SBP		–	–	–	0.07	00.04, 0.06	0.619	0.07	-0.04, 0.07	0.617
3MS	ARV SBP	62 - 1	-0.36	-0.80, -0.15	**0.005**	-0.33 0.14	-0.78, -0.10	**0.011**	-0.41	-0.87, -0.23	**0.001**
(*Overall cognition)*	Mean SBP	(Res>3)	–	–	–		-0.03, 0.10-	0.249	0.21-	-0.01, 0.11	0.079
Short-term BPV - sleep											
RTI – Md reaction time *(Psychomotor speed)*	ARV DBP	65	0.38	1.99, 8.29	**0.002**	0.32	0.99, 7.76	**0.012**	0.29	0.41, 7.34	0.029
	DBP mean		-	-	–	0.14	-0.48, 1.73	0.263	0.17	-0.41, 1.88	0.203
Short-term BPV - dipping											
MTT–Reaction latency	Dipper vs	59									
(Executive function)	Extreme		15.90*	-57.35, 89.15	0.665	14.58	-55.57, 84.73	0.378	0.33	-69.73, 70.39	0.993
	Non		83.22*	17.60, 148.63-	**0.014**	39.51	-40.61, 119.66	0.327	57.62	-23.21, 138.45	0.158
	Reverse		27.15*-		0.705	8.04	-138.68, 154.75	0.913	-26.45	-172.44, 119.55	0.717
	Mean SBP				–	0.41	-1.61, 2.43-	0.685	0.46	-1.60, 2.52	0.655
						-					
Day-to-day BPV – morning											
RTI –Movement time	ARV SBP	69	0.26	0.21, 3.96	0.030	0.21	-0.39, 3.69	0.112	0.18	-0.62, 3.55	0.166
(Psychomotor speed)	Mean SBP		-	–		0.12	-0.37, 0.96-	0.383-	0.11	-0.47, 1.02	0.469
SWM- Errors	ARV SBP	69	0.35-	0.18, 0.90-	**0.004**-	0.32	0.12, 0.87	**0.010**	0.32	0.11, 0.89	0.013
(Working memory)	Mean SBP					-0.01-	-0.12, 0.12-	0.966-	0.03	-0.13, 0.15	0.848
SWM-Strategy	ARV SBP	69	0.28-	0.02, 0.27	0.021	0.23	-0.01, 0.24	0.061	0.23	-0.01, 0.25	0.070
(Executive function)	Mean SBP			-	–	0.03-	-0.04, 0.05	0.787	0.03	-0.04, 0.05	0.860
Day-to-day BPV – evening											
MTT-Incorrect	ARV DBP	68 – 6	0.06-	-0.19, 0.31-	0.630-	0.14	-0.10,0.36	0.259	0.15	-0.08, 0.37	0.210
(Executive function)	Mean DBP				-	0.04-	-0.11, 0.15-	0.714-	0.07	-0.09, 0.17	0.567

*Note.*β values are standardised unless there is a * sign behind it then its unstandardised. Model1: Unadjusted, Model2: Adjusted for Age, mean BP, Model 3: Adjusted for Model 2+ Gender, BMI, AHT, Education

[#] Values have been upscaled by 100, Bold font highlights significant ($p<0.013$) values, AHT Anti-hypertensive treatment, ARV Average Real Variability, CI Confidence interval, DBP diastolic blood pressure, SBP systolic blood pressure, MTT Multitasking test, PAL Paired associate learning, RTI Reaction time task, rt reaction time, RVP Rapid visual information processing, SWM Spatial working memory.

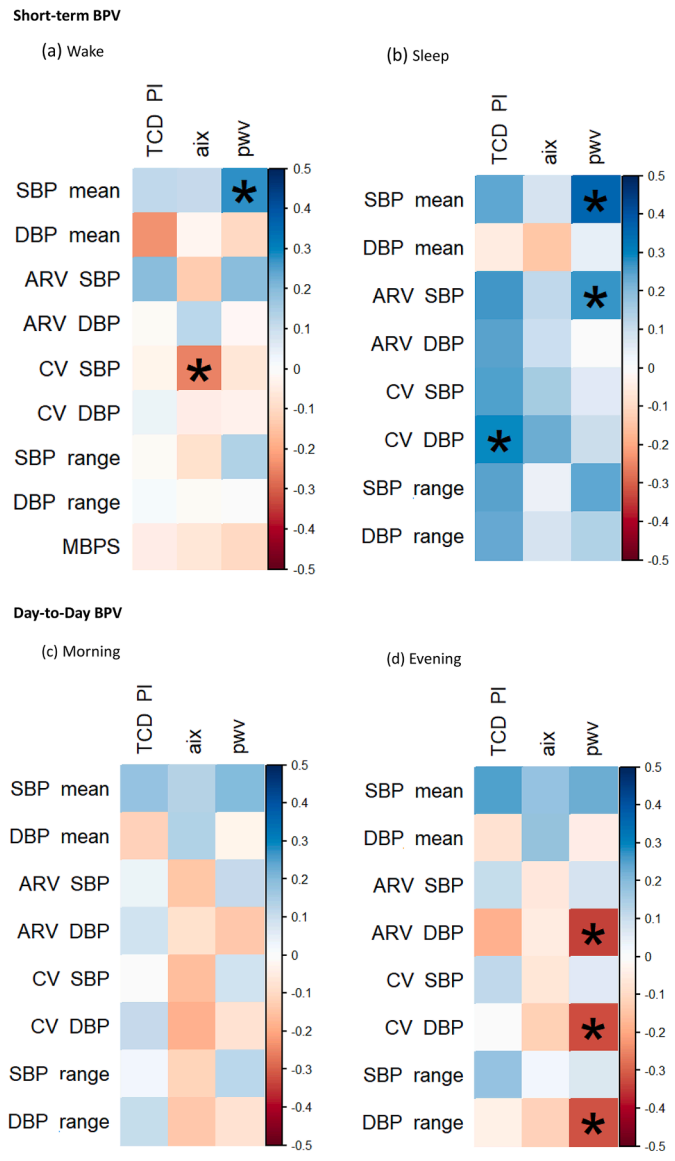

Fig. 3. Spearman correlations between systolic and diastolic blood pressure (BP) measures and vascular stiffness measure, with the colour illustrating the correlation coefficient r. *ARV* Average real variability, *aix* Augmentation index, *CV* Coefficient of variation, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PI* Pulsatility index, *pwv* pulse wave velocity, *TCD* Transcranial Doppler.

3.3.2. Day-to-Day blood pressure variability

3.3.2.1. Morning day-to-day BPV. None of the correlations between systolic or diastolic morning-to-morning BPV reached a statistically significant level, with negligible to small effect sizes (Fig. 3).

3.3.2.2. Evening day-to-day BPV. Higher diastolic evening-to-evening BPV was significantly associated with lower PWV in the Spearman correlation as well as across the adjusted linear regression models ($p=0.01$, $\beta = -0.29$). Systolic BPV showed no significant correlations with vascular stiffness measures with negligible effect sizes (Fig. 3).

4. Discussion

The current results show that higher BPV, independently of the mean BP, is linked with lower cognitive performance and to a smaller degree, with higher arterial stiffness, before clinically cognitive impairment is apparent in older adults. Systolic awake short-term BPV showed the largest number of significant negative associations with cognitive performance, particularly with sustained attention and overall cognition. In contrast to our hypothesis, we found no significant associations between short-term (awake or sleep) or day-to-day BPV (morning or evening) and cerebrovascular pulsatility. However, higher systolic short-term sleep BPV was linked with higher arterial stiffness (PWV) and higher diastolic day-to-day evening BPV was linked with lower arterial stiffness. The various patterns of associations between the BPV categories (e.g. short-term vs mid-term BPV) support the notion that specific BPV categories reflect different underlying biological mechanisms and likely play different roles in cognitive decline [13,50]. These findings highlight the role of systolic and diastolic BPV as a potential early clinical marker or treatment target for cognitive decline.

4.1. BPV and cognition

Our results indicate that BP fluctuations during the day and night might be more important for cognitive health than the mean BP or circadian BP patterns, in community dwelling older adults.There have been conflicting results regarding whether weighted 24 hours, day- or night-time BPV, or circadian patterns are associated with cognition. These discrepancies could be influenced by (i) variations in the used BPV metric, such as use of BPV metrics that are too heavily dependent upon the mean BP, and (ii) in differences on how cognition was assessed (e.g. different cognitive domains) or (iii) the investigated population (e.g. middle aged adults or older adults) [17]. The current study assessed wake and sleep BPV as well as the circadian BP patterns across a 24-hour window, within the same participant sample, and found different patterns of associations with cognition. Whilst higher wake and sleep-time BPV was significantly associated with lower cognitive test performance, contrary to our prediction, there were no significant associations present between night-time dipping or the morning blood pressure surge and cognitive measures. In support of our circadian BP findings, McDonals et al. [51], who also looked at an older community dwelling participant sample, reported no significant associations between the night-time dipping status and cognitive functioning. Hence, night-time dipping patterns might play a stronger predictive role in middle age or in people with sleep disorders. Nevertheless, further research is needed as within the current sample only a relatively small percentage of participants fell into the non-dipper or reverse dipper category.

Our results highlight the importance of looking at diastolic as well as systolic day and night-time BPV and suggest that a measurement of individual sleep BPV is more sensitive than a measurement of generic night-time BPV. Awake systolic short-term BPV was significantly negatively associated, after controlling for covariates, with sustained attention and general cognition (3MS). On the other hand, for BPV during sleep, there were no significant associations between systolic BPV but increased diastolic BPV was significantly associated with reduced psychomotor speed. In line with our results, Sakakura et al [52] and McDonals et al. [51], who also looked at a community dwelling older adult sample, found that increased systolic BPV during the day was associated with reduced overall cognitive functioning (assessed via the MMSE) but not during the night. McDonals et al [51] reported no significant associations between diastolic night-time BPV and cognition and Sakura et al. [52] only looked at systolic BPV. Notably, whilst our results found a significant association between sleep diastolic BPV (based on the sleep diary) and psychomotor speed, this association failed to reach a statistical significance level when looking at night-time BPV (22:00- 7:00). Hence, our results indicate that future studies that investigate BPV, should base the day/night classification upon the sleep status of the participants rather than on a pre-selected generic time. Variations in predictive values between night-time and day-time blood pressure variability (BPV) are commonly observed in the existing literature that has investigated the clinical significance of short-term BPV for cardiovascular events [53,54]. BPV during the day is influenced by BP

Table 4
Results for linear regressions with arterial stiffness (assessed via PWV) and middle cerebral arterial pulsatility as outcomes and BPV as predictor with covariates

			Model 1- unadjusted			Model 2- partially adjusted			Model 3 – fully adjusted		
Outcome	Predictor	N	β	CI [95%]	p	β	CI [95%]	p	β	CI [95%]	p
Short-term BPV - sleep											
Carotid- femoral Pulse	ARV SBP	57 - 1	0.29	0.01, 0.23	0.030	0.31	0.03, 0.23	0.015	0.30	0.03, 0.22	**0.012**
wave velocity (PWV)	Mean DBP		-			-0.12	-0.06, 0.02-	0.346-	-0.10	-0.06, 0.02	0.394
Short-term BPV - dipping											
Middle cerebral artery pulsatility index (PI)	Dipper vs	49-1									
	Extreme		-0.23*	-0.45, -0.01	0.039	-0.29*	-0.51, -0.06	0.013	-0.29*	-0.53, -0.05	0.018
	Non		0.03*	-0.14, 0.21	0.722	-0.06*	-0.26, 0.14	0.531	-0.05*	-0.26, 0.16	0.653
	Reverse		-0.14*	-0.66, 0.39	0.600	-0.17*	-0.69, 0.35	0.513	-0.15*	-0.70, 0.40	0.592
	Mean SBP					0.00*	-0.00, 0.01	0.121	0.00*	-0.00, 0.01	0.175
Carotid-femoral Pulse wave velocity (PWV)	Dipper vs	53 – 1									
	Extreme		0.10*	-1.17, 1.37	0.874	-0.37*	-1.51, 0.78	0.525	0.09	-1.05, 1.22	0.877
	Non		1.07*	0.01, 2.13	0.048	0.04*	-1.04, 1.12	0.944	0.02	-1.04, 1.07	0.975
	Reverse		1.82*	-0.39, 4.04	1.104	1.57*	-0.39, 3.53	0.113	1.90	0.03, 3.77	0.046
	Mean SBP					0.03*	-0.00, 0.06	0.071	0.02	-0.01, 0.05	0.206
Day-to-day BPV – evening											
Carotid-femoral Pulse wave velocity (PWV)	ARV DBP	56	-0.36	-0.34, -0.06	**0.006**	-0.34	-0.33, -0.06	**0.005**	-0.29	-0.29, -0.04	**0.011**
	Mean DBP		-	-	-	0.08	-0.04, 0.08	0.509	0.03	-0.05, 0.07	0.815

Note.β values are standardised unless there is a * sign behind it then its unstandardised. Model1: Unadjusted, Model2: Adjusted for Age, mean BP, Model 3: Adjusted for Model 2+ Gender, BMI, AHT, Education # Values have been upscaled by 100, Bold font highlights significant ($p<0.013$) values, ARV Average Real Variability, CI Confidence interval, DBP diastolic blood pressure, SBP systolic blood pressure.

changes in response to environmental factors (e.g physical activity levels), that are regulated by intrinsic cardiovascular regulatory mechanisms (e.g. arterial compliance and reflexes) [11]. Night-time BPV might be more reflective of the sympathetic drive and might be indicative of sleep apnoea [55]. Sleep apnoea is linked with a sympathetic overactivity, leading to increased peripheral vascular resistance [56], and is accompanied by changes in cardiac output. Whilst the current study excluded participants with a clinical diagnosis of obstructive sleep apnoea, no clinical assessments were undertaken to screen participants.

Morning as well as evening day-to-day BPV showed significant associations with executive functioning. Past research on day-to-day BPV has often only focused on morning measures [57–59]. Whilst our results showed significant associations between morning as well as evening day-to-day BPV and executive functioning, there were more associations, with stronger effect sizes, present in the morning than in the evening. Our results are in line with previous literature, that shows a link between increased day-to-day systolic and diastolic BPV and cognitive decline [58] and an increased dementia risk [57].

Systolic and diastolic BP are differently affected by age [18]. Systolic BP usually rises with age, whilst diastolic BP shows an increasing trend in middle-age but then a fall in later life (≥60), which can be linked back to age-related arterial stiffening [18,31]. Whilst there has been a strong focus on systolic BPV and clinical outcome measures [3], more recent research into long-term BPV has indicated that diastolic BPV also plays an independent and important role in cognitive decline, especially in people above the age of 60 [60]. However, further research is needed to better understand the role that diastolic BPV, particularly in short- and mid-term, plays in cognitive decline.

4.2. Blood pressure variability and vascular stiffness

Our results have shown that increased short-term systolic sleep BPV, but not diastolic BPV, is linked with increased arterial stiffness (PWV), and increased day-to-day evening diastolic BPV is negatively linked to arterial stiffness. This finding is in line with previous research that has looked at short-term BPV in hypertensive individuals, reporting a significant positive association between systolic BPV (across 24 hours) and arterial stiffness (PWV) [24–26]. It appears that systolic BPV shows stronger associations with arterial stiffening than diastolic BPV, for short [26] as well as long-term variability measures [61].

The pathophysiological differences in the mechanisms between systolic and diastolic BPV and cognitive decline, as well as with adverse cardiovascular outcomes, are still unclear [3]. However, a possible hypothesis is that high systolic BPV may be more reflective of vascular stiffness, whilst high diastolic BPV might be more linked with autonomic dysfunctions [3,62].

In line with our cognitive functioning findings, the current results of arterial stiffness suggest that the focus for intervention should more be on the variability of blood pressure, rather than the circadian patterns of BP. Whilst past research [28,29] has found significant associations between decreased BP dipping during the night and increased arterial stiffness in hypertensive samples, the current study found no such link. However, our results indicated that extreme dippers show a negative association with the pulsatility of the middle cerebral artery. Although there have been mixed findings across past literature in relation to extreme BP dipping being a predictor for cardiovascular risk [28,29], a recent study, looking at newly diagnosed hypertensive individuals reported that extreme dipping neither played an adverse nor favourable role in the development of hypertension-mediated organ damage [63]. Further, the study of Pucci et al.[27], found that the positive relationship between morning BP surge and arterial stiffness (PWV) was no longer present after accounting for systolic short-term BPV.

A proposed mechanism linking increased BPV with cognitive decline, is that high BPV translates to excessive cerebral blood flow fluctuations, exposing the brain to hyper- and hypotensive episodes, which in turn promote cerebrovascular impairments [2,64,65]. With advancing age, the cerebrovascular auto-regulatory mechanisms, that safeguard the cerebral microvasculature against fluctuations in blood pressure and ensure sufficient blood flow, become less efficient [66,67]. Hence, BPV might be of particular importance in older adults. In support of this theory, past research has shown that increased BPV is linked with white matter hyperintensities [7,32] reduced cortical thickness [68], as well as with lower cerebrovascular reactivity [69]. Further, it has been suggested that arterial stiffening can intensify these effects, as the transmission of the aorta BP to the arterioles in the brain is less dampened by stiffened vessels [33,70]. Increased cerebrovascular pulsatility might be a mediating factor in the relationship between BPV, cerebrovascular damage and dementia [33,71]. However, studies have not looked at the relationship between BPV measures and cerebrovascular pulsatility, which is linked with white matter hyperintensities [72,73]. Whilst the current study failed to find a statistically significant association between BPV measures and pulsatility, there was a medium effect size present in the correlation between short-term systolic BPV and the pulsatility index of the middle cerebral artery. Furthermore, the association between

mean systolic or diastolic BP and pulsatility was also not statistically significant. As the current participant sample was relatively healthy, the current study might be underpowered to establish a statistically significant relationship between BPV and pulsatility.

4.3. Strengths and weaknesses

A strength of the current study is that we used a comprehensive assessment of BPV including three different systolic and diastolic BPV metrics (CV, ARV and range). Interestingly, all three measures showed similar patterns of association, which suggests that they measure similar aspects of BPV. However, in line with previous research [46,48] ARV, especially for short-term BPV, showed stronger associations with cognition. Further, the current study provided a comprehensive assessment of cognitive functioning providing an understanding into the link between BPV and different cognitive domains rather than just overall cognition. However, there are also some limitations present. The current study had a relatively small sample size and used convenience sampling. Due to the non-random sampling technique, it is likely that the current sample had a higher level of education and cognitive functioning compared to a population-based sample [74,75]. Whilst TCD is a cost-effective measure to assess cerebrovascular pulsatility, TCD data is challenging to acquire in older adults, due to skull thickening causing a poor insonation window [76]. This has led to a reduced sample for the pulsatility assessment and may have resulted in us being underpowered to detect associations. Further, the current study only looked at the pulsatility index of the middle cerebral arteries. Hence, further research is necessary to understand the link between BPV and cerebrovascular pulsatility. It also needs to be noted that the current results are correlational and reverse- causation cannot be excluded, as it is possible that brain structural changes that are linked with cognitive decline, might cause increased BPV [2]. However, past animal studies [77,78] and longitudinal follow up studies [8,79] point towards the current hypothesised direction.

5. Conclusion

The current findings show that systolic and diastolic short- and mid-term BPV is negatively associated with cognitive functioning, independent of the mean BP. Short-term BPV appears to be associated with attention and psychomotor speed, whilst day-to-day BPV was mainly linked with executive functioning. BPV seems to be more sensitive in detecting associations with lower cognitive performance and arterial stiffening than circadian BP measures, in a cognitively unimpaired older adult population. Overall, this study has highlighted the importance of taking the variable nature of systolic and diastolic BP into consideration, when optimising the management of BP as a dementia risk factor.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Supplementary materials

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