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Visit-to-visit blood pressure variability and subthreshold depressive symptoms in older adults

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Abstract

Objectives: Depression is related to increased risk for dementia, possibly through links with cerebrovascular disease. Blood pressure variability is an emerging risk factor for cerebrovascular disease and dementia, but relationships with affective symptoms remain understudied.

Design: Retrospective analysis of prospective cohort study

Setting: Alzheimer's Disease Neuroimaging Initiative

Participants: 505 older adults without history of dementia or recent depression underwent 3–4 blood pressure measurements over 12 months and completed a self-report measure of depressive symptoms (Geriatric Depression Scale – 15 Item) at study baseline and 24-months follow-up.

Measurements: Blood pressure variability was calculated as variability independent of mean and maximum minus minimum. Regression models investigated relationships between blood pressure variability and severity of self-reported depressive symptoms at 24-months follow-up after controlling for several variables, including average blood pressure, antihypertensive use, antidepressant use, and baseline depressive symptom severity.

Results: Elevated diastolic blood pressure variability was related to greater total depressive symptom score at follow-up (ß = .16 [95% CI .02, .30]; $p = .03$), with specific contribution from increased severity of symptoms of dysphoria (odds ratio = 1.35 [95% CI 1.07, 1.75]; $p = .02$).

[†]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Author contributions

IJS designed and conceptualized the study. IJS analyzed the data. IJS and DAN interpreted the data. IJS drafted the manuscript for intellectual content. JYJ, DLS, and DAN revised the manuscript for intellectual content.

The data has not been previously presented orally or by poster at scientific meetings.

Blood pressure variability was not significantly related to other symptom subscales, including those reflecting life satisfaction or withdrawal.

Conclusions: Findings suggest that elevated diastolic blood pressure variability is related to subthreshold depressive symptomatology in older adults without history of dementia or recent depression, independent of average blood pressure. Blood pressure variability may be an understudied vascular risk factor linked with depression and cognitive impairment, with potential therapeutic implications.

Keywords

blood pressure variability; subthreshold depression; aging

OBJECTIVE

Several studies suggest that depression may increase the risk of dementia, including Alzheimer's disease (AD).[1] While potential mechanisms remain an area of active investigation, it has been hypothesized that cerebrovascular health may underlie changes in psychiatric and cognitive functioning.[1] Consistent with this hypothesis, growing evidence suggests that depression in late life is often comorbid with cerebrovascular disease and cognitive impairment.[1–3] Additionally, the relationship between depression and vascular risk factors, like hypertension, may be bidirectional, with therapeutic implications for cognitive impairment and mental health.[4]

Blood pressure (BP) control has garnered enormous attention with regard to brain health.[5] Beyond BP therapies that aim to control average levels, considering the variability in BP may improve cerebrovascular, cognitive, and affective outcomes.[6] Emotional, physical, and environmental factors all cause fluctuations in BP levels that occur over seconds to years.[6,7] A growing number of studies link elevated BP variability (BPV) with increased cerebrovascular disease burden,[6,8] cognitive impairment, and dementia, including incidence and progression of AD,[9,10] independent of and oftentimes above[9] average BP levels. Fewer studies investigate relationships with mood, and those that do suggest that increased BPV over the short-term (e.g., beat-to-beat, hours, days) is related to anxiety and depression.[11] The even more limited number of studies on long-term BPV (e.g., months, years, also called "visit-to-visit" BPV) are mixed, with one suggesting links with generalized anxiety disorder (GAD) but not major depression,[12] and the other suggesting that BPV interacts with late-life depression and cerebrovascular disease severity to predict cognition in older adults.[13] However, these two studies examined links with clinical diagnoses of GAD and/or major depression in older adults, but less is known about relationships with milder, subthreshold symptoms of depression. Importantly, investigating the role of visit-to-visit BPV in this range of affective symptoms may help elucidate increasingly studied relationships between vascular health, psychiatric symptoms, and cognitive impairment.[4] Examining this in older adult populations without history of dementia or recent depression could improve understanding of early changes, since affective symptoms that emerge in later life may represent early stages of a neurodegenerative process.[14,15] Findings would add to the limited number of studies on BPV and mood. The present study investigated the relationship between visit-to-visit BPV in older adults without history of dementia or recent depression

and symptoms of depression at one year follow-up, independent of average BP and baseline depressive symptoms.

METHODS

Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The ADNI study is a multisite natural history study that has collected clinical, biomarker, and neuropsychological data since 2003 to measure the progression of typical aging, mild cognitive impairment (MCI), and AD. Volunteer adults (age 55–91) were enrolled if they met the following criteria: few depressive symptoms at study baseline (Geriatric Depression Scale (GDS)[16] < 6), free of history of neurological disease (other than suspected AD), no greater than mild dementia symptoms (Clinical Dementia Rating scale ≤ 1), and low vascular risk (Hachinski Ischemic Score ≤ 4). Ethical approval was obtained for each institution involved and all participants provided written informed consent. Further study details can be found online (https://adni.loni.usc.edu).

The present study included participants who underwent clinical evaluation at study baseline and BP measurement at study screening, baseline, and 6- and 12- months follow-up. Participants also completed a self-report measure of depressive symptoms, the GDS-15,[16] at study screening and 24-months follow-up.

Measures

Clinical assessment—Baseline clinical evaluation identified participants to be cognitively normal (CN) or MCI, as described elsewhere.[17,18] All participants were confirmed to be without history of dementia or stroke. Briefly, participants were determined to be CN by ADNI criteria if they had a Mini Mental State Exam (MMSE) score > 24; Clinical Dementia Rating scale score of 0; without history of major depressive disorder within the past year, MCI, or dementia. A clinical diagnosis of MCI was given if the following ADNI criteria were met:[19] subjective memory complaint; Mini Mental State Exam (MMSE) scores between 24 and 30 (inclusive); global Clinical Dementia Rating scale score of 0.5; scores on delayed recall of Story A of the Wechsler Memory Scale Revised Logical Memory II subtest that are below expected performance based on years of education; did not meet criteria for a clinical diagnosis of AD. For the present analysis, CN and MCI participants were combined into one category of older adults without history of dementia or stoke.

BP assessment—Participants underwent seated BP measurement (taken from the dominant forearm arranged at the horizontal level of the fourth intercostal space at the sternum) 3–4 times between study screening and 12-months follow-up using a calibrated mercury sphygmomanometer, as described elsewhere.[17,18,20] Briefly, participants were instructed to refrain from conversation during and shortly before BP collection and were kept as calm and undisturbed as possible.

BP measurements were taken using the same device and BP cuff, by the same person, at the same time of day, where possible. Intraindividual BPV was calculated for each participant

using the 3–4 BP measurements collected over the 12-month period as variation independent of mean (VIM), a commonly used index of visit-to-visit BPV that is uncorrelated with average BP levels across visits[8,17,18,21] and better predicts all-cause mortality compared to other indices of BPV.[22] VIM was calculated as: VIM = SD/mean^x, where the power x was derived from non-linear curve fitting of BP SD against average BP using the nls package in R,[23] as described elsewhere.[21] BPV was also calculated as maximum minus minimum (MMM) BP.[7] Baseline hypertension status was determined from the total sample average systolic BP taken at study baseline.

Depression assessment—At study baseline and 24-months follow-up, participants completed the GDS-15,[16] a validated self-report measure of depressive symptoms in older adult populations.[24] The GDS-15 was adapted from the longer GDS-30 and includes the items with the highest correlation with depressive symptoms.[25] The GDS-15 contains 15 "yes-no" questions about the presence or absence of symptoms experienced over the past week. GDS-15 total scores range from 0–15 and clinical severity is determined as follows: minimal 0–4; mild 5–8; moderate 9–11; severe 12–15.[25] Several studies have determined depressive subscales from both the GDS-30 and GDS-15 using factor analysis.[24,26] The GDS-15 was divided into three distinct depressive symptom subscales as previously described:[24] General Depressive Affect/Dysphoria (e.g., "Do you feel that your situation is hopeless?"), Life Satisfaction ("Are you in good spirits most of the time?"), and Withdrawal ("Have you dropped many of your activities or interests?"). Lifetime history of depression was determined from baseline medical history and was defined as at least one major depressive episode at least one year prior to study enrollment (i.e., to meet inclusionary criteria for the ADNI study), as described elsewhere.[27]

Other measurements—Several demographic and clinical variables were determined from baseline clinical evaluation: global cognition (i.e., MMSE score), body mass index (BMI, weight [kg] / height [m] squared), use of antihypertensive medication, and use of antidepressant medication. Participants were categorized at those taking antihypertensive medication (all classes) versus those who were not, and those taking antidepressant medication versus those who were not. Vascular risk was also determined from baseline clinical evaluation using criteria derived from the Framingham Stroke Risk Profile,[28] which was previously shown to correlate with cerebrovascular disease burden.[29] Specifically, baseline clinical evaluation determined the presence/absence of individual risk factors: history of cardiovascular disease, history of diabetes mellitus type 2, history of atrial fibrillation, history of carotid artery disease, history of transient ischemic attack (TIA)/ subclinical stroke. Participants were categorized as having lower (≤ 1 vascular risk factor) or higher (≥ 2 vascular risk factors) vascular risk.[28] Apolipoprotein (APOE) ϵ4 carrier status was determined from baseline venipuncture as previously described[30] and participants were categorized as those with at least one APOE ϵ4 allele versus those without.

Data availability statement—All data are available on the ADNI site (https://adni.loni.usc.edu).

Statistical Analysis

First, multiple linear regression was used to examine the relationship between BPV and GDS-15 total score at 24-months follow-up (e.g., 12 months after BPV was determined). Next, ordinal logistic regression was used to investigate relationships between BPV and specific depressive symptom subscales at 24-months follow-up. Relationships with systolic BPV and diastolic BPV were examined separately. All models included the following covariates: age at follow-up, sex, antihypertensive medication use, antidepressant medication use, vascular risk (lower vs higher), BMI, average BP, and GDS-15 total score at study baseline. Sensitivity analyses additionally controlled for 1) lifetime history of depression, 2) MMSE score, 3) baseline hypertension status, and 4) APOE ϵ4 carrier status. All analyses were 2-tailed with significance set at $p < .05$ or effect estimates with confidence intervals excluding 0 (multiple linear regression) or 1 (ordinal logistic regression). The following are reported for results of multiple linear regression analyses: standardized regression coefficient/standardized beta (ß), 95% confidence interval, *p*-value, delta R squared (ΔR^2), degrees of freedom, and *F*-value for the overall model. The following are reported for results of ordinal logistic regression analyses: odds ratio (OR), 95% confidence interval, *p*-value, Wald chi-square χ^2, and degrees of freedom. All analyses were carried out in R Project.[23]

RESULTS

A total of 505 participants with BPV over 12 months (e.g., study screening through 12-months follow-up) and valid GDS-15 at baseline and 24-months follow-up were included in the final study sample. Table 1 summarizes clinical and demographic information. Importantly, the average GDS-15 total score at baseline was 1.2 (1.3 SD), and scores ranged from 0 – 5, consistent with ADNI enrollment exclusionary criteria of GDS-15 scores >= 6. Therefore, the present study only included participants with low levels of depressive symptoms at study baseline. BPV was not significantly correlated with average BP levels (systolic: $t(\text{df} = 502) = .04$; $p = 35$; n = 504; diastolic: $t(\text{df} = 502) = .02$; $p = .74$; n = 504), consistent with the definition of VIM.[21]

BPV and total depressive symptoms

Multiple linear regression revealed that elevated diastolic BPV was significantly related to increased GDS-15 total score at follow-up, independent of GDS-15 total score at study baseline (VIM: standardized regression coefficient/standardized beta (ß) = .16 [95% CI .02, .30]; $p = .03$; $\Delta R^2 = .007$; df = 477; $F(9, 477) = 22.8$; MMM: ß = .15 [95% CI .01, .30]; $p = .04$; $\Delta R^2 = .007$; df = 476; $F(9, 476) = 22.7$) (Figure 1). Systolic BPV was not significantly related to GDS-15 total score at follow-up (VIM: ß = .11 [95% CI −.03, .25]; $p = .13$; $\Delta R^2 = .003$; df = 476; MMM: ß = .10 [95% CI −.04, .25]; $p = .16$; $\Delta R^2 = .003$; df = 475) (data not shown).

BPV and distinct depressive symptom subscales

In ordinal logistic regression analyses, increased diastolic BPV was significantly related to higher Dysphoria subscale score (VIM: odds ratio (OR) = 1.35 [95% CI 1.07, 1.75]; $p = .02$; Wald chi-square χ^2 (1, 490) = .30; MMM: OR = 1.40 [95% CI 1.07, 1.80]; $p = .01$; χ^2 (1, 489) = .04) (Figure 2). No significant relationships were observed between systolic

BPV and Dysphoria subscale score (VIM: OR = .97 [95% CI .90, 1.04]; $p = .44$; χ^2 (1, 490) = −.03; MMM: OR = .94 [95% CI .70, 1.24]; $p = .68$; χ^2 (1, 489) = −.004), or between BPV and severity of any other GDS-15 depressive symptom subscale (Withdrawal: diastolic: VIM: OR = 1.05 [95% CI .91, 1.22]; $p = .48$; χ^2 (1, 490) = .06; MMM: OR = 1.03 [95% CI .86, 1.24]; $p = .76$; χ^2 (1, 489) = .002; systolic: VIM: OR = 1.02 [95% CI .97, 1.07]; $p = .40$; χ^2 (1, 490) = .02; MMM: OR = 1.00 [95% CI .99, 1.02]; $p = .68$; χ^2 (1, 489) = .003; Life Satisfaction: diastolic: VIM: OR = .89 [95% CI .78, 1.02]; $p = .09$; χ^2 (1, 490) = −.02; MMM: OR = .98 [95% CI .92, 1.04]; $p = .76$; χ^2 (1, 489) = −.02; systolic: VIM: OR = 1.03 [95% CI .98, 1.07]; $p = .26$; χ^2 (1, 490) = −.03; MMM: OR = 1.09 [95% CI .92, 1.30]; $p = .99$; χ^2 (1, 489) = −.01).

Findings remained significant in sensitivity analyses controlling for 1) lifetime history of depression (GDS-15 total score: VIM: ß = .16 [95% CI .02, .30]; $p = .03$; $\Delta R^2 = .007$; df = 475; MMM: ß = .15 [95% CI .01, .29]; $p = .04$; $\Delta R^2 = .006$; df = 474; Dysphoria subscale score: VIM: OR = 1.47 [95% CI 1.09, 2.04]; $p = .03$; χ^2 (1, 489) = .30; MMM: OR = 1.40 [95% CI 1.08, 1.81]; $p = .01$; χ^2 (1, 489) = .04), 2) MMSE score (GDS-15 total score: VIM: ß = .16 [95% CI .02, .30]; $p = .03$; $\Delta R^2 = .007$; df = 474; MMM: ß = .16 [95% CI .01, .30]; $p = .03$; $\Delta R^2 = .007$; df = 474; Dysphoria subscale score: VIM: OR = 1.46 [95% CI 1.08, 2.02]; $p = .02$; χ^2 (1, 490) = .29; MMM: OR = 1.38 [95% CI 1.06, 1.79]; $p = .01$; χ^2 (1, 489) = .04), 3) baseline hypertension status (GDS-total score: VIM: ß = .16 [95% CI .02, .30]; $p = .03$; $\Delta R^2 = .007$; df = 474; MMM: ß = .15 [95% CI .01, .30]; $p = .03$; $\Delta R^2 = .006$; df = 474; Dysphoria subscale score: VIM: OR = 1.47 [95% CI 1.09, 2.04]; $p = .02$; χ^2 (1, 490) = .29; MMM: OR = 1.39 [95% CI 1.07, 1.81]; $p = .01$; χ^2 (1, 489) = .04) and 4) APOE ϵ4 carrier status (GDS-15 total score: VIM: ß = .16 [95% CI .02, .31]; $p = .03$; $\Delta R^2 = .007$; df = 475; MMM: ß = .15 [95% CI .01, .30]; $p = .04$; $\Delta R^2 = .006$; df = 475; Dysphoria subscale score: VIM: OR = 1.46 [95% CI 1.08, 2.03]; $p = .02$; χ^2 (1, 490) = .29; MMM: OR = 1.39 [95% CI 1.07, 1.80]; $p = .01$; χ^2 (1, 489) = .04).

DISCUSSION

Study findings suggest elevated visit-to-visit BPV is related to higher total depressive symptom score with specific contribution from increased severity of the Dysphoria subscale. Importantly, these findings were in a study sample without history of dementia or recent depression, indicating BPV may be related to subthreshold levels of depression in the absence of major neurocognitive dysfunction. Findings add to the literature on subthreshold levels of depression in aging and dementia.[31]

A growing number of studies suggest comorbidity of depression, cerebrovascular disease, and cognitive impairment in older adults.[1,4] One possibility is that cerebrovascular disease may drive both affective symptoms and cognitive change.[32] There is strong evidence that elevated BPV is related to severity and progression of cerebrovascular disease as assessed by MRI-based markers (e.g., white matter hyperintensities, cortical infarcts, cerebral microbleeds)[6] and postmortem evaluation (e.g., atherosclerosis in the Circle of Willis, cerebral arteriolosclerosis, lacunes).[8] Chronic high fluctuations in BP may distend arterial walls beyond repair, creating a sort of “tsunami effect”[33] in the cerebral parenchyma. While the quickly increased pressure may shock arterial walls and disrupt the tight

junctions of the blood-brain-barrier,[6,7] the receding pressure may increase the risk of cerebral hypoperfusion,[18] especially in brain regions vulnerable to fluctuating BP levels such as the subcortical white matter and hippocampi. Vascular burden has been associated with psychomotor slowing and executive dysfunction, which rely heavily on frontal-subcortical systems.[34] Importantly, these are also hallmark neuropsychological features of depression, and early neurodegenerative disease processes are often misdiagnosed as depression.[35] Therefore, BPV may contribute to cerebrovascular disease severity, which is in turn powerfully linked with depressive symptoms,[1–3] possibly through disruption of frontal-subcortical and limbic networks regulating mood, affect, and motivation. The central autonomic network, comprised of the periaqueductal gray matter, parabrachial nucleus, nucleus tractus solitarius, ventrolateral medulla, hypothalamus, amygdala, and insula, regulates the human cardiovascular system and is critical in modulating responses to emotional stimuli.[7] Elevated BPV might be associated with depressive symptoms via dysregulation of the central autonomic network. While the present study is cross-sectional in nature (BPV associated with depressive symptoms at 24-months), depressive symptomatology was assessed after the measurement of BPV, indicating BPV may be a vascular risk factor linked with the development of depressive symptoms before the onset of advanced cognitive change. Future studies are needed to disentangle the temporal order of relationships between BPV, depressive symptomatology, and cognitive impairment.

Interestingly, diastolic BPV, and not systolic BPV, was related to depressive symptoms. Some evidence suggests that diastolic BPV predicts cerebrovascular disease lesion burden better than systolic BPV.[6,8] Additionally, while systolic BPV has been hypothesized to reflect arterial stiffness, diastolic BPV is thought to reflect endothelial dysfunction, baroreflex sensitivity, or sympathetic autonomic nervous system over-activation/reactivity to environmental exposures,[9] the latter of which is critically linked with affective symptoms.[36] Depression may also be related to endothelial dysfunction and sympathetic dysregulation in the context of cerebrovascular disease.[37] Incorporating the variability of BP into antihypertensive treatment planning could have the potential to benefit brain health. Some classes of antihypertensive medications have differential effects on BP in risk for stroke, independent of traditionally studied average BP levels.[38] While the current study was not able to address this possibility as it relates to depressive symptoms, elucidating potential class effects may have therapeutic implications.

Findings add to the limited number of studies investigating visit-to-visit BPV and depression in older adults,[12,13] and improve our understanding of associations with subthreshold levels of depressive symptoms. For an increase of 1 SD in diastolic BPV, there was a 35% −40% increased odds of having greater symptoms of dysphoria, depending on the index of BPV used, suggesting a relatively small effect. However, even a small effect may be important since the present analysis controlled for baseline depressive symptoms, major depression was excluded, and participants had only subthreshold depressive symptoms. Furthermore, present findings suggest specific contribution from the Dysphoria subscale, which includes questions about hopelessness that have been linked to increased suicidal ideation and risk of suicide attempts.[39] The study is strengthened by assessment of depressive symptoms at study baseline and after the determination of BPV. BPV was determined from BP measurements obtained from methods standard in routine clinical

practice and may represent an index of vascular health readily accessible in primary care settings. Study limitations include the fact that some aspects of BP measurement were not standardized across sites, which could introduce measurement error. BPV is impacted by a variety of physiological and psychological factors (e.g., stimulant intake, medication use, pain, perceived stress), not all of which were able to be controlled for in the present study. Despite this, visit-to-visit BPV determined using similar methods has consistently been linked with cognitive impairment, cognitive decline, incidence and progression of dementia, stroke, cerebrovascular disease, and several other outcomes.[6,9] Therefore, the extension of these findings to subthreshold depressive symptoms using similar methods adds to the literature in this area. GDS-15 total scores were low at baseline and follow-up, precluding investigation of relationships in study samples with a broader range of depressive symptoms. Relatedly, participants in the present study had a range of normal to mild levels of cognitive impairment and relationships with depressive symptoms may be different in individuals with more advanced cognitive impairment. Additionally, the majority of the study sample was non-Hispanic White with limited cerebrovascular disease (Hachinski Ischemic Score ≤ 4), which limits generalizability of findings to more diverse samples and those with greater cerebrovascular disease burden. No corrections were made for multiple comparison, which could inflate risk for Type 1 errors. Finally, although the reliability of BPV remains unclear and may weaken effect sizes, at least one study indicates BPV is reproducibly related to cardiovascular risk (i.e., stroke, heart attack),[40] and a large body of evidence indicates BPV is related to cardiovascular and cerebrovascular outcomes.[6,7]

CONCLUSIONS

Findings suggest elevated BPV in older adults without history of dementia or recent depression is related to greater depressive symptoms at follow-up, independent of average BP levels. BPV may be a useful marker of vascular dysfunction with potential therapeutic implications for brain health in older adults.

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Conflicts of interest

IJS, JYJ, and DAN report no conflicts with any product mentioned or concept discussed in this article. DLS has received research support from NIH and Eisai, has participated as a paid member of a DSMB or adjudication committee with Acadia, Avanir, Janssen, and Otsuka, and has received consulting fees from Avanir and NovoNordisk.

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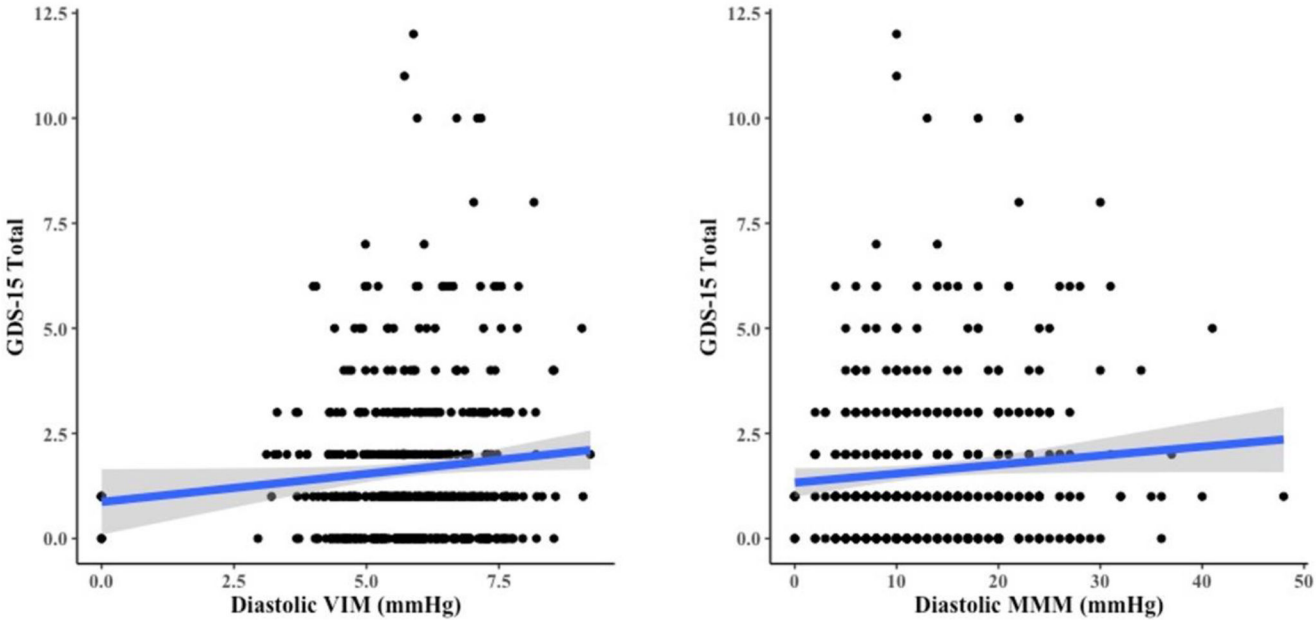

Figure 1. Elevated diastolic BPV is related to total depressive symptom score

Scatterplots display the results of the linear regression between diastolic BPV (VIM and MMM) and GDS-15 total score at 24-months follow-up. 95% confidence interval is shaded around the regression lines.

Abbreviations: BPV = blood pressure variability: GDS-15 = Geriatric Depression Scale – 15 Item; VIM = variability independent of mean; MMM = maximum minus minimum

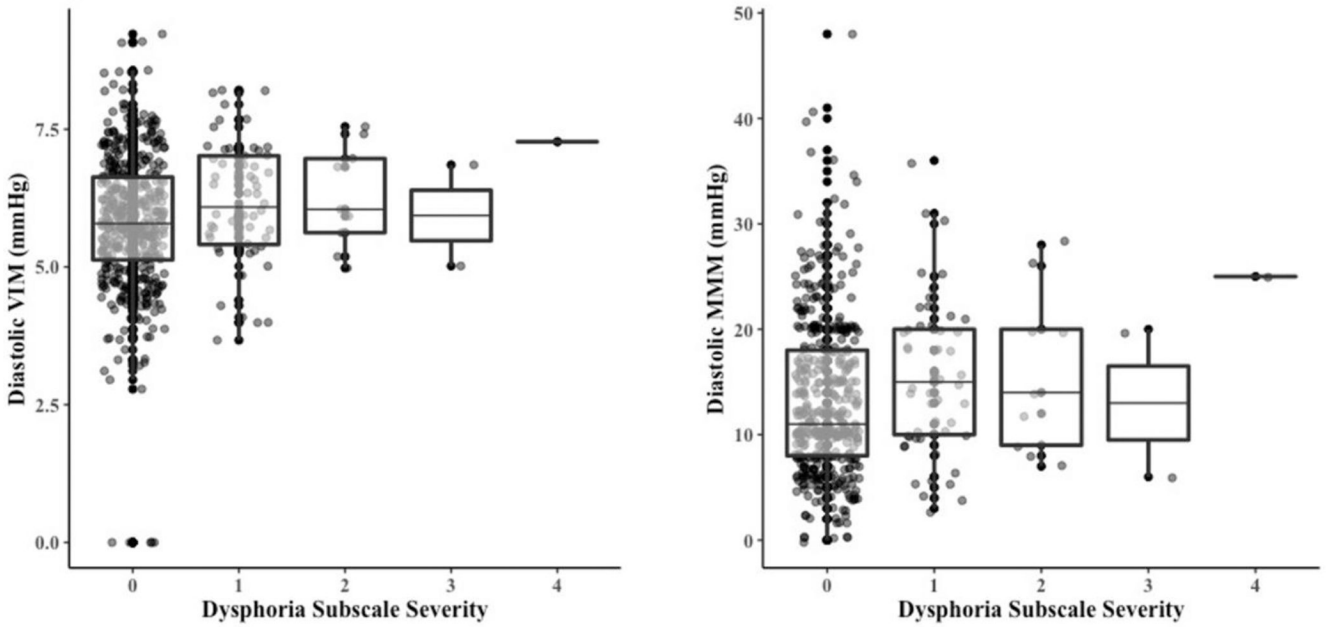

Figure 2. Elevated diastolic BPV is related to severity of Dysphoria subscale

Boxplots display the results of the ordinal logistic regression of diastolic BPV (VIM and MMM) predicting the severity of Dysphoria subscale.

Abbreviations: BPV = blood pressure variability; VIM = variability independent of mean; MMM = maximum minus minimum

Table 1.

Baseline clinical and demographic information.

	Total sample (*N* = 505)
Age (years)	77.7 (6.5)
Sex (*n*, % female)	204 (40.4%)
Education (years)	15.9 (2.9)
APOE ϵ4 carriers (*n*, %)	221 (43.8%)
ADNI MCI diagnosis (*n*, %)	303 (60.0%)
Lifetime history of depression (*n*, %)	118 (23.4%)
MMSE score	27.9 (1.8)
GDS-15 (baseline)	
Total score	1.2 (1.3)
Dysphoria subscale	0.04 (range: 0–1)
Withdrawal subscale	0.2 (range: 0–1)
Life satisfaction subscale	0.7 (range: 0–1)
GDS-15 (24-months follow-up)	
Total score	1.7 (1.9)
Dysphoria subscale	0.2 (range: 0–4)
Withdrawal subscale	0.6 (range: 0–3)
Life satisfaction subscale	2.3 (range: 0–4)
BMI (kg/m^2)	26.4 (4.2)
Vascular risk [*] (*n*, % lower)	470 (93.1%)
Vascular risk factors (*n*, %)	
Cardiovascular disease	16 (3.2%)
Diabetes mellitus type 2	7 (1.4%)
Atrial fibrillation	6 (1.2%)
Carotid artery disease	3 (0.6%)
TIA/subclinical stroke	4 (7.9%)
Medication use (*n*, %)	
Antihypertensive agents	216 (42.8%)
ACE inhibitors	69 (13.7%)
ARBs	41 (8.1%)
Alpha blockers	18 (3.6%)
Calcium channel blockers	49 (9.7%)
Diuretics	31 (6.1%)
Antidepressant agents	99 (19.6%)
Systolic BP (mmHg)	
Baseline	135.2 (17.4)
Average	133.9 (13.5)
VIM	5.4 (3.9)
MMM	23.5 (12.7)
Diastolic BP (mmHg)	

	Total sample (*N* = 505)
Baseline	74.3 (9.9)
Average	73.6 (7.7)
VIM	5.9 (1.3)
MMM	13.6 (7.4)

Means and SDs shown unless otherwise indicated.

* Baseline vascular risk level determined from presence/absence of individual risk factors (history of cardiovascular disease, history of diabetes mellitus type 2, history of atrial fibrillation, history of carotid artery disease, history of TIA/subclinical stroke). Risk level is lower (≤ 1 individual vascular risk factor) or higher (≥ 2 individual vascular risk factors), as described elsewhere.[24,37,38]

Abbreviations: MMSE = Mini Mental State Exam; BP = blood pressure; BMI = body mass index: VIM = variability independent of mean; MCI = mild cognitive impairment; CDR-sb = Clinical Dementia Rating Scale sum of box score; ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; ADNI = Alzheimer's Disease Neuroimaging Initiative; TIA = transient ischemic attack; GDS-15 = Geriatric Depression Scale – 15 Item; MMM = maximum minus minimum