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Psychiatric correlates of blood pressure variability in the elderly: The Three City cohort study

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HIGHLIGHTS

- Modifiable factors associated with BPV are still being established.
- 1454 elderly participants underwent HBPM and serial BP measures over 8 years.
- GAD was associated with systolic BPV over 8 years.
- The GAD association with systolic BPV was consistent for morning and evening measures.
- GAD but not depression was associated with increased systolic BPV over 8 years.

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ABSTRACT

Background: The modifiable factors associated with blood pressure variability (BPV) are still being established and their clinical relevance is poorly understood. Generalized anxiety disorder (GAD) and depression have been implicated with higher BPV in the short term (e.g. hours, days) however their effects on BPV over longer periods are unknown.
Methods: In a prospective cohort study, 1454 elderly participants (age 78.5 ± 3.78 years, 59% women) underwent structured interview for GAD and major depression. Participants performed home blood pressure monitoring (HBPM) over 3 consecutive days and underwent serial clinic BP measures on 4 separate follow-ups over an 8 year period. Systolic and diastolic BPV was calculated using the coefficient of variation (CV) and standard deviation method. Generalized linear models assessed the association between GAD and depression with BPV over an 8 year period.
Results: GAD was associated with significantly increased systolic BPV over 8 years in age, sex and mean systolic BP ($\beta = 0.25$, SE = 0.09; $p = 0.007$) and fully adjusted models ($\beta = 0.23$, SE = 0.10; $p = 0.017$). BPV from HBPM was strongly associated with 8 year systolic BPV in age-sex ($\beta = 3.10$, SE = 0.82; $p < 0.001$) and fully adjusted models ($\beta = 3.09$, SE = 0.84; $p < 0.001$). The association between GAD and longer term BPV was consistent when analyzing morning and evening HBPM measures of BPV. There was no association between diastolic BPV over 8 years with GAD or depression.
Conclusions: GAD but not depression was associated with increased systolic BPV over an 8 year period controlling for HBPM. GAD has clinical relevance for control of systolic BPV in elderly participants.

1. Introduction

Blood pressure (BP) varies within individuals over time [1]. An increase in BP variability (BPV) is an emerging focus in clinical and epidemiological studies because of links to incident and recurrent stroke [2–4] and major cardiovascular outcomes [5–8] independent of mean systolic BP. The clinical relevance of BPV beyond the effects of mean BP remains controversial and poorly understood [7,9]. Increased BPV is associated with decreased arterial compliance and complex parasympathetic, behavioral and psychological processes [1,10]. It is unclear which factors leading to higher BPV can be modified, if any. Among potentially modifiable risk factors, generalized anxiety disorder (GAD) and major depression have been implicated with higher BPV in the short term (e.g. hours and days) [11–13], however their effects on BPV over longer periods (i.e. years) is lesser reported. Clarifying the long term association between GAD, major depression and BPV is imperative

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because persons with these disorders have higher healthcare costs [14] and are at a high risk of stroke and cardiovascular events [15–19]. Moreover, BPV is one plausible mechanism portending an increased cardiovascular morbidity risk [2,20].

A body of empirical work documents the cross-sectional association between depression and anxiety with BPV derived from beat-to-beat, ambulatory and home BP measures [11–13,21]. One limitation of the extant evidence is the paucity of longitudinal research describing how GAD and depression relate to BPV measured over longer periods. This is necessary to clarify because of the longer intervals whereby BP is typically measured in clinical practice [22] and the equivocal findings as to whether BPV increases or decreases over time [22–25]. A second limitation of the extant research is the use of predominantly younger and healthy participants who are at a lower stroke risk than elderly populations. This is an important limitation to reconcile since both GAD and major depression are among the most common psychiatric disorders in elderly persons [26,27].

The current study adds to the extant literature by examining BPV in relation to GAD and major depression in a prospective cohort of elderly individuals who underwent home blood pressure monitoring (HBPM) on three consecutive days, and clinic visits over 8 years. The aim of this study was to assess the association between GAD and major depression with BPV over an 8 year period, controlling for HBPM BPV.

2. Materials and methods

2.1. Population

The Three-City (3C) Study is a French prospective cohort study investigating the determinants of stroke and dementia [28]. Briefly, 9294 noninstitutionalized community dwelling adults aged 65 years or older were recruited and underwent baseline neurological examinations. The cohort was monitored for major cardiovascular disease and neurological outcomes. The current analyses use only participants from the Dijon center at the 2nd wave of follow-up who were invited to participate in a HBPM study. Serial follow-up was performed thereafter at years 2, 5, and 8. Persons with confirmed stroke history were excluded because GAD and depression are more common in the post-stroke period [29] and BPV may decline over time after stroke. From 2085 participants invited to participate in HBPM, 1814 agreed (87% acceptance rate), 1737 had at least 12 HBPM readings and 1454 returned for the 8 year follow-up. Participants who were not eligible for the study or lost to follow-up were generally older, more likely female and lower BMI, and less likely to have cardiovascular disease, otherwise characteristics were similar. The study protocol has been approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and each participant provided signed and informed consent (Fig. 1).

2.2. Blood pressure measurement and variability

The methods of HBPM have been reported previously [30]. Briefly, at the study center, participants were given instructions on how to measure their own BP with the validated digital electronic tensiometer OMRON M4 (OMRON Corp., Kyoto, Japan). They had one individual supervised demonstration, and they were assigned the same device for use at home. A booklet with simplified instructions and a logbook to record their BP measures were also provided. HBPM was scheduled on 3 consecutive days and participants instructed to record their BP 3 times in the morning and 3 times in the evening (6 readings p/day up to a maximum of 18 HBPM readings). Each of the three BP measures were separated by 2 min after the subject rested at least 5 min in a seated position, with an adaptable sized cuff placed on the left arm. Morning measures had to be performed <1 h after awaking and before taking any drug. Evening measures had to be realized close to bedtime. Patients were asked to keep a record of all BP readings in a logbook.

Clinic BP was measured according to a standardized protocol after at least 5 min of rest in a seated position, with an appropriately sized cuff placed on the left arm. Clinic visits were performed prior to HBPM, and again at year 2, 5, and 8. Participants BP was measured in the left arm (3 readings p/year up to a maximum of 12 BP readings). BPV was calculated separately for HBPM and clinic visits. BPV was calculated using 3 methods with possible prognostic association with stroke [31].

Coefficient of variation: $CV = \frac{SD}{Mean}$

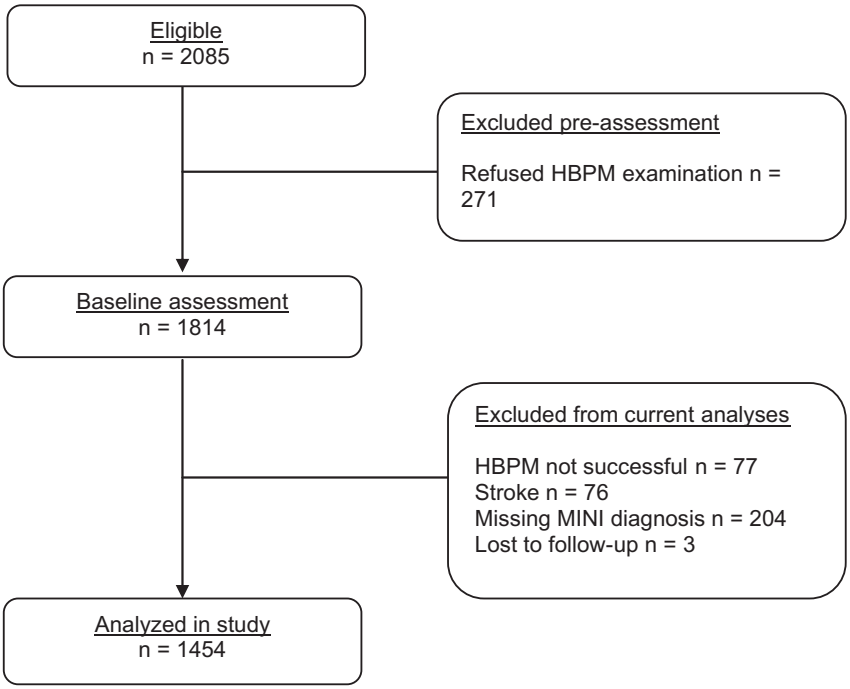

Fig. 1. Flow chart of participants through the study.

Standard Deviation: $SD = \sqrt{\sum_{i=1}^{n} \frac{(yi-y)2}{(n-1)}}$ where n = the number of observations, y_i = the systolic BP for a given individual at each visit, and y = the individual's mean BP across all observations. The study results were consistent with the two methods and the SD results can be found in the online supplement (eTable 1, eTable 2, eTable 3).

2.3. Assessment of anxiety and depression disorder

Participants underwent a structured clinical interview with the MINI International Neuropsychiatric Interview [32]. The MINI has established psychometric validity for affective disorders including inter-rater agreement and concurrent validity with other structured clinical interviews [33,34]. For brevity, only the GAD, major depression and dysthymia modules were administered and no hierarchical exclusion rules were adopted thus permitting depression and GAD comorbidity. Very few participants met dysthymia criteria in the cohort (n = 6), and thus this disorder was not considered further in this study.

2.4. Assessment of drug exposure

Medications use during the preceding month was determined at interview, and, where feasible, the medications themselves were seen by the interviewer. The name of the medication was recorded, and all drugs were subsequently coded according to the French translation of the WHO ATC classification [35]. Drug use for BP was explicitly differentiated from use for other cardiovascular diseases [36]. Drug classes were; alpha-blockers, beta-blockers, calcium channel blockers, thiazide diuretics, angiotensin converting enzyme inhibitors and angiotensin-II receptor blockers. Psychotropic medication was recorded and included anti-depressants (serotonin reuptake inhibitors, tri- and tetra-cyclics) and benzodiazepines. No participants were using monoamine oxidase inhibitors.

2.5. Assessment of covariates

Participants underwent face-to-face interviews using a standardized questionnaire with trained interviewers covering demographic characteristics, daily life habits and medical history. Assessment of the number of alcoholic drinks, tobacco and coffee consumption was collected by a designated survey with the Mini Nutritional Assessment [37] as reported elsewhere [38]. Diabetes was defined as medication use for diabetes or fasting plasma glucose ≥7.0 mmol/L. Comorbidities were classified according to international classification of disease criteria and included cardiovascular disease (myocardial infarction, coronary artery bypass or percutaneous intervention, peripheral vascular disease and stroke). Persons who reported the occurrence of cardiovascular events during follow-up further medical data were obtained from general practitioners, specialists and hospital records [39]. The diagnosis and classification of cardiovascular events was made according to International Classification of Diseases 10th revision criteria.

2.6. Statistical analyses

Continuous data are represented as mean and SD or median and interquartile range (IQR) as appropriate. The characteristics of participants were compared according to follow-up status, GAD and major depression with independent sample *t*-tests, chi-square and Wilcoxon-Mann-Whitney tests depending on variable distribution. A log transformation was applied to the BPV data because of skewed distribution. The association between HBPM BPV and clinic BPV was modeled with curve fitting to determine the most appropriate fit based on R^2 and F values. We proceeded with a generalized linear model (GLM) with a normal-identity distribution and maximum likelihood estimation using Wald criteria.

Each GLM entered GAD and major depression into the model with age, sex and mean BP (over 8 years). In the second model we added covariates; hypertension or antihypertensive drug use for hypertension, CVD, diabetes, BMI, hypercholesterolemia, smoking, alcohol and coffee consumption. There was no association between arrhythmia or pacemaker insertion and BP and thus these were not included in any model. In the final model we added anti-depressant and benzodiazepine use. We repeated the main analysis stratifying by morning and evening measures of BP during the HBPM adjusted for all covariates. In ancillary models we stratified by the presence of a dichotomized hypertension variable defined as systolic BP >140 mmHg or diastolic BP >90 mmHg or use of antihypertensive medication for BP. Ancillary analyses adjusted for all covariates apart from psychotropic medication as the ratio of covariates to participants in the model was too low. All analyses were performed with PASW version 22.0, a p value ≤ 0.05 was considered as statistically significant. No adjustment was made for multiple comparisons using the guidelines outlined by Rothman [40].

3. Results

The final sample includes 1454 participants with a mean age of 78.5 ± 3.8 years and was comprised of 59% women. At baseline there were 82/1454 persons with depression (5.64% of total) and 84/1454 persons with GAD (5.78% of total). A comparison of participants based on GAD and depression status is shown in Table 1. Participants with GAD were more likely to be antihypertensive drug users and have major depression. Participants with depression were more likely to be female, have GAD, and have lower systolic BP for mean, morning and evening measures as well as lower BPV using the SD method.

3.1. Association between GAD and depression with 8 year systolic BPV

GAD was significantly associated with 8 year BPV in age, sex and mean systolic BP adjusted models ($\beta = 0.25$, SE = 0.09; $p = 0.007$). Adjustment for covariates and psychotropic medication use only marginally attenuated the strength of the association between GAD and 8-year BPV. Major depression was not significantly associated with systolic BPV. Systolic BPV derived from HBPM was strongly associated with 8 year BPV in the models (Table 2).

3.2. Morning and evening HBPM and 8 year systolic BPV

The morning HBPM model suggested that GAD was associated with significantly increased systolic BPV over 8 years in age, sex and mean systolic BP ($\beta = 0.24$, SE = 0.09; $p = 0.01$) and fully adjusted models. Systolic BPV measured in the morning was significantly associated with BPV at 8 years ($\beta = 0.33$, SE = 0.08; $p < 0.001$). A similar pattern of results was evident with the evening systolic HBPM measures, demonstrating a significant association between GAD and 8 year BPV in the age, sex and mean systolic BP ($\beta = 0.26$, SE = 0.09; $p = 0.006$) and fully adjusted models. Systolic BPV measured in the evening was significantly associated with BPV at 8 years ($\beta = 0.16$, SE = 0.06; $p = 0.009$) but to a lesser extent than the morning BPV measure.

3.3. Association between GAD and depression with 8 year diastolic BPV

There was no association between diastolic BPV with GAD or major depression (eTable 3). Diastolic BPV derived from HBPM was strongly associated with 8 year BPV in the models using the CV and SD method.

3.4. Ancillary model in hypertensive participants

Analyses stratified by baseline hypertension showed that GAD was significantly associated with 8 year systolic BPV among the population with hypertension ($\beta = 0.25$, SE = 0.10; $p = 0.012$). There was no association in the non-hypertensive population.

Table 1
Descriptive characteristics of the sample based on GAD and depression status at baseline (n = 1454).

Variable	No GAD n = 1370	GAD n = 84	p	No Depression n = 1372	Depression n = 82	p
Female sex	810 (59.1)	58 (69.0)	0.072	804 (58.6)	64 (78.0)	<0.001
Age in years, M ± SD	78.5 ± 3.8	78.0 ± 3.6	0.27	78.5 ± 3.8	77.9 ± 3.4	0.18
Anti-hypertensive drug use	803 (58.5)	59 (70.2)	0.035	815 (59.4)	47 (57.3)	0.71
Systolic BP mmHg, M ± SD	142.0 ± 16.7	142.7 ± 17.4	0.71	142.4 ± 16.7	136.5 ± 16.9	0.002
Morning systolic BP mmHg, M ± SD	143.9 ± 18.5	144.9 ± 20.3	0.61	144.3 ± 18.6	137.5 ± 18.6	0.001
Evening systolic BP mmHg, M ± SD	140.2 ± 17.2	140.5 ± 16.7	0.87	140.5 ± 17.1	135.7 ± 17.3	0.016
Diastolic BP mmHg, M ± SD	73.6 ± 8.8	73.2 ± 9.3	0.70	73.7 ± 8.8	72.3 ± 9.1	0.16
Morning diastolic BP mmHg, M ± SD	75.4 ± 9.5	75.2 ± 10.5	0.83	75.5 ± 9.5	73.6 ± 9.9	0.09
Evening diastolic BP mmHg, M ± SD	71.9 ± 9.1	71.2 ± 9.1	0.50	71.9 ± 9.1	70.8 ± 9.0	0.29
CV Systolic BP, M ± SD	8.1 ± 2.9	8.3 ± 2.5	0.65	8.2 ± 2.9	7.7 ± 2.4	0.12
CV Diastolic BP, M ± SD	8.3 ± 3.6	8.7 ± 3.7	0.31	8.3 ± 3.6	8.4 ± 4.2	0.83
Cardiovascular disease	97 (7.1)	8 (9.5)	0.40	100 (7.3)	5 (6.1)	0.69
Hypercholesterolemia	527 (38.5)	31 (36.9)	0.78	529 (38.6)	29 (35.4)	0.56
Diabetes	130 (9.5)	12 (14.3)	0.15	135 (9.8)	7 (8.5)	0.70
Body mass index, M ± SD	26.7 ± 3.9	25.9 ± 4.4	0.74	26.7 ± 3.8	26.1 ± 3.9	0.82
Median alcoholic drinks g p/day (IQR)	5.8 (0–13.0)	2.7 (0–11.0)	0.11	5.5 (0–13.0)	4.1 (0–9.6)	0.35
Tobacco smoking, never	817 (59.6)	54 (64.3)	0.45	814 (59.3)	57 (69.5)	0.046
Former	501 (36.6)	27 (32.1)		504 (36.7)	24 (29.3)	
Current	52 (3.8)	3 (3.6)		54 (3.9)	1 (1.2)	
Median coffee intake p/week (IQR)	1 (0–2)	1 (0–2)	0.19	1 (0–2)	1 (0–2)	0.98
Psychiatric disorder[1]	57 (4.2)	25 (29.8)	<0.001	59 (4.3)	25 (30.5)	<0.001

GAD, generalized anxiety disorder; IQR, interquartile range;
[1] Psychiatric disorder variable refers to MDD in analysis of GAD groups, and vice versa.

4. Discussion

In this prospective cohort study GAD was associated with systolic BPV over 8 years. The significant association between GAD and systolic BPV was generally consistent when adjusted for covariates, psychotropic medication, and utilizing morning and evening HBPM measures. Together, the findings points to the general consistency in association between GAD and 8-year systolic BPV. Secondly, the results demonstrate a significant association between HBPM with BPV over an 8-year period, as this association was evident for systolic and diastolic HBPM BPV.

Both GAD and major depression have been linked with hypertension in epidemiological studies [41,42] and associated with higher BPV in the short term [11–13,21]. Here depression was associated with lower systolic BPV using the SD method which parallels findings that depression may lead to decreased systolic BP in older populations [43]. In contrast to depression, GAD was only associated with systolic BPV over 8 years and not during HBPM. Our results generally contrast to prior studies demonstrating cross-sectional links between negative emotions and short term BPV or baroflex control [11–13]. The discrepancy between our findings with prior research could be explained by the longer follow-up and different method of ascertaining BPV, given that BPV assessed by different methods and timeframes may reflect a broad range of phenomena [44]. This is the first study to assess GAD and depression in relation to BPV over an 8 year period. Other methodological differences include the larger sample size and recruitment of an older population here that were characterized by substantial comorbidities. Another important methodological difference relates to our sampling which was restricted to participants able to perform HBPM themselves [30] whereas other studies have derived BPV from 24-h BP monitoring. Our findings are potentially biased towards GAD because depression is associated with a reduced ability to perform HBPM [30]. Although GAD and depression are both associated with increased sympathetic drive and arterial stiffness [45,46], these psychiatric disorders may differ in behavioral characteristics important to BP control. For example, depression is associated with non-adherence to prescription drugs [47] and lower adherence to antihypertensive medication is one purported mechanism of higher BPV over long periods [7,9,48]. By contrast, GAD and its hallmark symptom of worry may be associated with increased adherence to prescription drugs and other cardiovascular health recommendations [49]. Given that antihypertensive drug adherence is a key behavioral mechanism of increased BPV [1,10], it is striking that GAD was associated with higher systolic BPV over an 8 year period.

Another part of this study was assessing the link between HBPM and 8 year clinic BPV. The extant literature has largely documented BPV in placebo-controlled trial settings of antihypertensive drugs [2,3,20,50] and the relevance of BPV to the general population is only more recently being explored [22–24]. Our results demonstrating a strong association between HBPM and 8 year BPV parallel McDonald et al.'s [23] findings. Recently McDonald et al. [23] found that 24-h, day and night BPV was significantly increased at 10 year follow-up independent of age, sex and medication despite stable mean BP. In contrast, Goldstein et al.

Table 2
Association between generalized anxiety disorder and major depression with 8 year systolic blood pressure variability (n = 1454).

CV method of BPV[1]	Model 1 age-sex adjusted			Model 2 + covariates			Model 3 + psychotropic medication		
	B	SE	p	β	SE	p	β	SE	p
Home blood pressure monitoring BPV[2]	3.10	0.82	<0.001	3.08	0.84	<0.001	3.09	0.84	<0.001
Generalized anxiety disorder	0.25	0.09	0.007	0.23	0.10	0.015	0.23	0.10	0.017
Major depression	0.11	0.09	0.26	0.11	0.09	0.25	0.09	0.09	0.36

BPV, blood pressure variability; CV, coefficient of variation; GLM, general linear model; HBPM, home blood pressure monitoring; SD, standard deviation; SE, standard error.
[1] In each model the dependent variable was long term systolic BPV and the independent variable included CV BPV from each participants' HBPM adjusted for: Model 1: age, sex and mean systolic BP, Model 2: additionally adjusted or cardiovascular disease, diabetes, antihypertensive drug use, BMI, hypercholesterolemia, alcohol consumption, coffee consumption, tobacco smoking, Model 3: additionally adjusted for anti-depressant and benzodiazepine use.
[2] A maximum of 18 systolic BP measures were recorded over 3 consecutive days at home (3 measures recorded in the morning, 3 measures recorded in the evening). Subjects were included in the analysis if they had at least 12 systolic BP readings at home over 3 consecutive days.

Table 3
Association between depression and generalized anxiety disorder with systolic BPV stratified by morning and evening BP readings[1].

Time of HBPM measure	Model 1 age-sex adjusted			Model 2 + covariates			Model 3 + psychotropic medication		
Morning	β	SE	p	β	SE	p	β	SE	p
Home blood pressure monitoring BPV[2]	0.33	0.08	<0.001	0.33	0.08	<0.001	0.33	0.08	<0.001
Generalized anxiety disorder	0.24	0.09	0.01	0.22	0.10	0.02	0.21	0.10	0.028
Major depression	0.11	0.10	0.24	0.12	0.10	0.22	0.09	0.10	0.36
Evening									
Home blood pressure monitoring BPV[2]	0.16	0.06	0.009	0.16	0.06	0.01	0.16	0.06	0.01
Generalized anxiety disorder	0.26	0.09	0.006	0.23	0.10	0.016	0.23	0.10	0.018
Major depression	0.11	0.09	0.26	0.12	0.09	0.23	0.10	0.10	0.33

BP, blood pressure; BPV, blood pressure variability; CV, coefficient of variation; GLM, general linear model; HBPM, home blood pressure monitoring; SD, standard deviation; SE, standard error.

[1] In each model the dependent variable was long term systolic BPV and the independent variable included CV BPV which was calculated from each participants' morning or evening HBPM adjusted for: Model 1: age, sex and mean systolic BP, Model 2: additionally adjusted or cardiovascular disease, diabetes, antihypertensive drug use, BMI, hypercholesterolemia, alcohol consumption, coffee consumption, tobacco smoking, Model 3: additionally adjusted for anti-depressant and benzodiazepine use.

[2] A maximum of 18 systolic BP measures were recorded over 3 consecutive days at home (3 measures recorded in the morning, 3 measures recorded in the evening). Subjects were included in the analysis if they had at least 12 systolic BP readings at home over 3 consecutive days.

[24] found that BPV decreased over a 5 year follow-up in 130 healthy adults using a hierarchical regression analysis. Weak correlations between ambulatory BPV indices have also been reported for up to 15 years follow-up [22]. The divergence in findings demonstrates the longer term correlates of BPV are still being established and lack of consensus on how best to calculate BPV.

The pathophysiological mechanisms through which BPV leads to cardiovascular risk are complex. In a broad sense BPV is a physiological marker of autonomic nervous system control [44]. Specifically, higher BPV is theorized to relate to compensatory hemodynamic changes associated with decreased arterial compliance, aortic stiffness and pressure wave reflection which lead to increased central aortic pressures [51]. Evidence from animal studies corroborates that higher BPV activates the renin–angiotensin–aldosterone system, leads to inflammation and produces lesions of arterial endothelial cells [52]. The implications of these BPV related effects on the cerbrovasculature is likely related to alterations in hemodynamics and the progression of cerebral small vessel disease [20]. The abovementioned pathophysiological mechanisms are documented in anxiety and depression populations. Anxiety is associated with systolic BPV and a leading mechanism is increased sympathetic modulation led by a reduction in baroreflex sensitivity [13]. Moreover beat-to-beat BPV parallels the spectral components of HRV [13], and a large body of work demonstrates that HRV is diminished in depression [53] and anxiety disorders [54]. Specifically, changes to low frequency power of BPV and HRV are suspected to relate to changes in central sympathetic nervous system control [55] (Table 3).

The clinical implications of ours, and parallel findings [31], are that a reduction in BPV should be considered alongside total BP management strategies in the elderly. Moreover, among the potentially modifiable risk factors for BPV, GAD was strongly associated with systolic BPV over 8 years in elderly participants raising the possibility that GAD treatment and symptom management may reduce BPV and consequently lower total stroke risk. However, given that psychosocial interventions alone do not necessarily improve BP [56], more aggressive BP management strategies could be considered contemporaneously with GAD treatment.

The strengths of this study include a large and well defined elderly cohort who performed HBPM [30]. The limitations of this study include that we did not calculate the proportion of variance explained in each model. Also, we only utilized 3 days of HBPM and included persons who did not meet criteria for hypertension. We did not evaluate shorter intervals of BPV (e.g. beat-to-beat) which may have more prognostic utility than HBPM to determine clinically relevant outcomes such as end organ damage [9]. Also there is no consensus as to the optimal methodology for calculating BPV. Though correlations are typically higher for CV than SD methods [2], both methods have prognostic value for stroke risk [31]. Another limitation is that we only obtained depression disorder and GAD status at baseline and did not serially reassess participants for changes in psychiatric disorder status. This could be important as the HUNT study demonstrated that persistently high depression and anxiety symptoms are associated with decreases in systolic and diastolic blood pressure over 22 years follow-up [43]. A related point is that we cannot rule out other unmeasured biases that affect longer term BPV including reduced adherence, improper dosing/titration of antihypertensive drugs, and seasonal changes [1,10]. Another aspect to consider is that the prevalence of depression here was above the 3.3% pooled estimate in a recent meta-analysis of persons aged ≥50 years [57]. By contrast, the prevalence of GAD here exceeds the 2.3% pooled estimate for current GAD in elderly populations [57]. Finally, it is unknown how long-term BPV, GAD and depression relate to the established stress-induced blood pressure reactivity paradigm. This hypothesis posits that individuals who exhibit large and frequent increases in BP during psychological stress are at risk of hypertension [58].

5. Conclusions

In conclusion, GAD was associated with systolic BPV over 8 years in this prospective cohort study. The association between GAD and 8 year systolic BPV was consistent after adjusting for HBPM BPV, antihypertensive drug use and covariates. Together, the findings points to the general consistency in association between GAD and longer term BPV. GAD is a potentially modifiable risk factor for increased systolic BPV in the elderly, and its treatment alongside BP may reduce total stroke risk.

Conflict of interest

Phillip J. Tully reports no conflict of interest. Christophe Tzourio reports no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.physbeh.2016.10.024.

References

[1] G. Parati, J.E. Ochoa, C. Lombardi, G. Bilo, Assessment and management of blood-pressure variability, Nat. Rev. Cardiol. 10 (2013) 143–155.
[2] P.M. Rothwell, S.C. Howard, E. Dolan, E. O'Brien, J.E. Dobson, B. Dahlof, et al., Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension, Lancet 375 (2010) 895–905.
[3] A.J. Webb, U. Fischer, Z. Mehta, P.M. Rothwell, Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis, Lancet 375 (2010) 906–915.
[4] Y. Hata, Y. Kimura, H. Muratani, K. Fukiyama, Y. Kawano, T. Ashida, et al., Office blood pressure variability as a predictor of brain infarction in elderly hypertensive patients, Hypertens. Res. 23 (2000) 553–560.
[5] K.K. Lau, Y.K. Wong, K.C. Teo, R.S. Chang, K.H. Chan, S.F. Hon, et al., Long-term prognostic implications of visit-to-visit blood pressure variability in patients with ischemic stroke, Am. J. Hypertens. 27 (2014) 1486–1494.
[6] P. Palatini, G. Reboldi, L.J. Beilin, E. Casiglia, K. Eguchi, Y. Imai, et al., Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the ambulatory blood pressure-international study, Hypertension 64 (2014) 487–493.
[7] E. Dolan, E. O'Brien, Is it daily, monthly, or yearly blood pressure variability that enhances cardiovascular risk? Curr. Cardiol. Rep. 17 (2015) 93.
[8] G. Parati, G. Mancia, Blood pressure variability as a risk factor, Blood Press. Monit. 6 (2001) 341–347.
[9] K. Asayama, F.F. Wei, Y.P. Liu, A. Hara, Y.M. Gu, R. Schutte, et al., Does blood pressure variability contribute to risk stratification? Methodological issues and a review of outcome studies based on home blood pressure, Hypertens. Res. 38 (2015) 97–101.
[10] A. Whaley-Connell, J.R. Sowers, Metabolic control of blood pressure variability in humans, J. Clin. Hypertens. (Greenwich) 18 (2016) 25–26.
[11] D.M. Davydov, D. Shapiro, I.A. Cook, I. Goldstein, Baroreflex mechanisms in major depression, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31 (2007) 164–177.
[12] B. Symonides, P. Holas, M. Schram, J. Sleszycka, A. Bogaczewicz, Z. Gaciong, Does the control of negative emotions influence blood pressure control and its variability? Blood Press. 23 (2014) 323–329.
[13] R. Virtanen, A. Jula, J.K. Salminen, L.M. Voipio-Pulkki, H. Helenius, T. Kuusela, et al., Anxiety and hostility are associated with reduced baroreflex sensitivity and increased beat-to-beat blood pressure variability, Psychosom. Med. 65 (2003) 751–756.
[14] L. Gentil, H.M. Vasiliadis, M. Préville, D. Berbiche, Impact of mental disorders on the association between adherence to antihypertensive agents and all-cause healthcare costs, J. Clin. Hypertens. (Greenwich). (2016) (in press).
[15] M. Li, X.W. Zhang, W.S. Hou, Z.Y. Tang, Impact of depression on incident stroke: a meta-analysis, Int. J. Cardiol. 180 (2015) 103–110.
[16] P.J. Tully, S.M. Cosh, H. Baumeister, The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease, J. Psychosom. Res. 77 (2014) 439–448.
[17] A. Pan, O.I. Okereke, Q. Sun, G. Logroscino, J.E. Manson, W.C. Willett, et al., Depression and incident stroke in women, Stroke 42 (2011) 2770–2775.
[18] R. Pequignot, C. Tzourio, K. Peres, M.L. Ancellin, M.C. Perier, P. Ducimetiere, et al., Depressive symptoms, antidepressants and disability and future coronary heart disease and stroke events in older adults: the three city study, Eur. J. Epidemiol. 28 (2013) 249–256.
[19] B.D. Jani, J. Cavanagh, S.J.E. Barry, G. Der, N. Sattar, F.S. Mair, Relationship between blood pressure values, depressive symptoms, and cardiovascular outcomes in patients with cardiometabolic disease, J. Clin. Hypertens. (Greenwich) 18 (10) (2016) 1027–1035.
[20] P.M. Rothwell, Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension, Lancet 375 (2010) 938–948.
[21] V.K. Yeragani, M. Mallavarapu, R.K. Radhakrishna, M. Tancer, T. Uhde, Linear and nonlinear measures of blood pressure variability: increased chaos of blood pressure time series in patients with panic disorder, Depress. Anxiety 19 (2004) 85–95.
[22] Z. Li, H. Snieder, G.A. Harshfield, F.A. Treiber, X. Wang, A 15-year longitudinal study on ambulatory blood pressure tracking from childhood to early adulthood, Hypertens. Res. 32 (2009) 404–410.
[23] C. McDonald, M.S. Pearce, J. Wincenciak, S.R. Kerr, J.L. Newton, Ambulatory blood pressure variability increases over a 10-year follow-up in community-dwelling older people, Am. J. Hypertens. (2015).
[24] I.B. Goldstein, D. Shapiro, D. Guthrie, A 5-year follow-up of ambulatory blood pressure in healthy older adults, Am. J. Hypertens. 16 (2003) 640–645.
[25] S. Gao, H.C. Hendrie, C. Wang, T.E. Stump, J.C. Stewart, J. Kesterson, et al., Redefined blood pressure variability measure and its association with mortality in elderly primary care patients, Hypertension 64 (2014) 45–52.
[26] C.S. MacKenzie, K. Reynolds, K.L. Chou, J. Pagura, J. Sareen, Prevalence and correlates of generalized anxiety disorder in a national sample of older adults, Am. J. Geriatr. Psychiatry 19 (2011) 305–315.
[27] E. Richard, C. Reitz, L.H. Honig, N. Schupf, M.X. Tang, J.J. Manly, et al., Late-life depression, mild cognitive impairment, and dementia, JAMA Neurol. 70 (2013) 374–382.
[28] The 3C Study Group, Vascular factors and risk of dementia: design of the three-city study and baseline characteristics of the study population, Neuroepidemiol 22 (2003) 316–325.
[29] A. Leppavuori, T. Pohjasvaara, R. Vataja, M. Kaste, T. Erkinjuntti, Generalized anxiety disorders three to four months after ischemic stroke, Cerebrovasc. Dis. 16 (2003) 257–264.
[30] C. Cacciolati, C. Tzourio, C. Dufouil, A. Alperovitch, O. Hanon, Feasibility of home blood pressure measurement in elderly individuals: cross-sectional analysis of a population-based sample, Am. J. Hypertens. 25 (2012) 1279–1285.
[31] C. Tai, Y. Sun, N. Dai, D. Xu, W. Chen, J. Wang, et al., Prognostic significance of visit-to-visit systolic blood pressure variability: a meta-analysis of 77,299 patients, J. Clin. Hypertens. (Greenwich) 17 (2015) 107–115.
[32] D.V. Sheehan, Y. Lecrubier, K. Sheehan, P. Amorim, J. Janavs, E. Weiller, et al., The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, J. Clin. Psychiatry 59 (1998) 22–33.
[33] Y. Lecrubier, D.V. Sheehan, E. Weiller, P. Amorim, I. Bonora, K.H. Sheehan, et al., The MINI international neuropsychiatric interview (M.I.N.I.) a short diagnostic structured interview: reliability and validity according to the CIDI, Eur. Psychol. 12 (1997) 224–231.
[34] D.V. Sheehan, Y. Lecrubier, K. Harnett-Sheehan, J. Janavs, E. Weiller, L.I. Bonora, et al., Reliability and validity of the MINI international neuropsychiatric interview (M.I.N.I.): according to the SCID-P, Eur. Psychol. 12 (1997) 232–241.
[35] World Health Organization, Guidelines for ATC Classification and DDD Assignment, Norwegian Institute of Public Health, Oslo, Norway, 2002.
[36] P.J. Tully, S. Debette, J.F. Dartigues, C. Helmer, S. Artero, C. Tzourio, Antihypertensive drug use, blood pressure variability, and incident stroke risk in older adults: three-city cohort study, Stroke 47 (2016) 1194–1200.
[37] Y. Guigoz, B. Vellas, P.J. Garry, Assessing the nutritional status of the elderly: the mini nutritional assessment as part of the geriatric evaluation, Nutr. Rev. 54 (1996) S59–S65.
[38] M.J. Torres, C. Feart, C. Samieri, B. Dorigny, Y. Luiking, C. Berr, et al., Poor nutritional status is associated with a higher risk of falling and fracture in elderly people living at home in France: the three-city cohort study, Osteoporos. Int. 26 (2015) 2157–2164.
[39] A. Alpérovitch, T. Kurth, M. Bertrand, M.-L. Ancelin, C. Helmer, S. Debette, et al., Primary prevention with lipid lowering drugs and long term risk of vascular events in older people: population based cohort study, BMJ 350 (2015) h2335.
[40] K.J. Rothman, No adjustments are needed for multiple comparisons, Epidemiology 1 (1990) 43–46.
[41] D. Carroll, A.C. Phillips, C.R. Gale, G.D. Batty, Generalized anxiety and major depressive disorders, their comorbidity and hypertension in middle-aged men, Psychosom. Med. 72 (2010) 16–19.
[42] N. Schmitz, W. Thefeld, J. Kruse, Mental disorders and hypertension: factors associated with awareness and treatment of hypertension in the general population of Germany, Psychosom. Med. 68 (2006) 246–252.
[43] B. Hildrum, U. Romild, J. Holmen, Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway, BMC Public Health 11 (2011) 1–8.
[44] M.C. Irigoyen, K. De Angelis, F. Dos Santos, D.R. Dartora, B. Rodrigues, F.M. Consolim-Colombo, Hypertension, blood pressure variability, and target organ lesion, Curr. Hypertens. Rep. 18 (2016) 31.
[45] A.J. Grippo, A.K. Johnson, Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models, Stress 12 (2009) 1–21 (Amsterdam, Netherlands).
[46] L.L. Ma, D.G. Kong, X.W. Qi, L.X. Wang, Generalized anxiety disorder and the circadian rhythm of blood pressure in patients with hypertension, Int. J. Psychiatry Clin. Pract. 12 (2008) 292–295.
[47] M.R. DiMatteo, H.S. Lepper, T.W. Croghan, Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence, Arch. Intern. Med. 160 (2000) 2101–2107.
[48] P. Muntner, E.B. Levitan, C. Joyce, E. Holt, D.L. Mann, S. Oparil, et al., Association between antihypertensive medication adherence and visit-to-visit variability of blood pressure, J. Clin. Hypertens. (Greenwich) 15 (2013) 112–117.
[49] G. Parker, M. Hyett, D. Hadzi-Pavlovic, H. Brotchie, W. Walsh, GAD is good? Generalized anxiety disorder predicts a superior five-year outcome following an acute coronary syndrome, Psychiatry Res. 188 (2011) 383–389.
[50] A.J. Webb, P.M. Rothwell, Effect of dose and combination of antihypertensives on interindividual blood pressure variability: a systematic review, Stroke 42 (2011) 2860–2865.
[51] G.F. Mitchell, Arterial stiffness and wave reflection: biomarkers of cardiovascular risk, Artery research 3 (2009) 56–64.
[52] D.F. Su, Treatment of hypertension based on measurement of blood pressure variability: lessons from animal studies, Curr. Opin. Cardiol. 21 (2006) 486–491.
[53] A.H. Kemp, D.S. Quintana, K.L. Felmingham, S. Matthews, H.F. Jelinek, Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk, PLoS One 7 (2012), e30777.
[54] J. Chalmers, D.S. Quintana, M.J. Abbott, A.H. Kemp, Anxiety disorders are associated with reduced heart rate variability: a meta-analysis, Front. Psychol. 5 (2014).

[55] G. Piccirillo, S. Elvira, C. Bucca, E. Viola, M. Cacciafesta, V. Marigliano, Abnormal passive head-up tilt test in subjects with symptoms of anxiety power spectral analysis study of heart rate and blood pressure, Int. J. Cardiol. 60 (1997) 121–131.
[56] S.J. Mann, Psychosomatic research in hypertension: the lack of impact of decades of research and new directions to consider, J. Clin. Hypertens. (Greenwich) 14 (2012) 657–664.
[57] J. Volkert, H. Schulz, M. Härter, O. Wlodarczyk, S. Andreas, The prevalence of mental disorders in older people in western countries – a meta-analysis, Ageing Res. Rev. 12 (2013) 339–353.
[58] K.A. Matthews, C.R. Katholi, H. McCreath, M.A. Whooley, D.R. Williams, S. Zhu, et al., Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study, Circulation 110 (2004) 74–78.