Psychological Medicine

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The association between systolic blood pressure variability with depression, cognitive decline and white matter hyperintensities: the 3C Dijon MRI study

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Original Article

Cite this article: Tully PJ, Debette S, Tzourio C (2018). The association between systolic blood pressure variability with depression, cognitive decline and white matter hyperintensities: the 3C Dijon MRI study. *Psychological Medicine* **48**, 1444–1453. https://doi.org/10.1017/S0033291717002756

Received: 27 October 2016
Revised: 16 August 2017
Accepted: 24 August 2017
First published online: 27 September 2017

Key words:
Blood pressure; blood pressure variability; depression; geriatric psychiatry; mild cognitive impairment; white matter hyperintensity

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Abstract

Background. Accumulating evidence links blood pressure variability (BPV) with white matter hyperintensities (WMH) and stroke. The longitudinal association between BPV with late onset depression (LOD) and cognitive decline remains unexplored.

Methods. Prospective cohort study of 2812 participant's age ⩾65 years (median age 72 years, 63.6% female) without dementia or stroke. Serial clinic visits assessed blood pressure, cognitive function, depression disorder, and depressive symptoms. A brain magnetic resonance imaging (MRI) substudy was performed in 1275 persons to examine possible associations with WMH.

Results. The interaction between symptomatic LOD and systolic BPV was associated with cognitive decline on the Isaac Set Test [slope −4.45; 95% confidence interval (CI) −8.92 to −0.16, $p = 0.04$], Benton Visual Retention Test (slope −0.89; 95% CI −1.77 to −0.01, $p = 0.049$), Mini Mental State Examination (slope −1.08; 95% CI −1.86 to −0.30, $p = 0.007$) and Finger Tapping Test (slope −7.53; 95% CI −13.71 to −1.34, $p = 0.017$) but not Trail Making Test-A or -B/A. The MRI substudy demonstrated that systolic BPV was associated with cognitive decline via interactions with depression and total WMH volume, but this was not dependent on either deep or periventricular WMH volumes.

Conclusions. The findings show that the interaction between systolic BPV with symptomatic depression and WMH increases cognitive decline in persons ⩾65 years of age. Future work could extend these findings by examining systolic BPV in relation to cognitive decline and WMH in older populations with depression.

Introduction

Research consistently demonstrates that visit-to-visit blood pressure variability (BPV) elevates the risk for stroke independent of mean systolic BP (Webb *et al.* 2010). A more recent body of work indicates that BPV is associated with cognitive decline (Sabayan *et al.* 2013) and dementia (Alperovitch *et al.* 2014) but the clinical relevance of BPV remains controversial (Dolan & O'Brien 2015). Depression is also associated with BPV in the short-term (e.g. beat-to-beat, hourly measures) (Virtanen *et al.* 2003; Scuteri *et al.* 2009; Symonides *et al.* 2014) however the effect over longer periods remains unknown (Nagai *et al.* 2012; Sabayan *et al.* 2013; Yano *et al.* 2014; Conway *et al.* 2015). Surprisingly, no previous study has contemporaneously examined the longitudinal effects of BPV on cognitive decline and depression especially in older cohorts.

Among the clinical presentations of depression, late onset depression (LOD) is frequently comorbid with cerebrovascular disease (CVD), and cognitive dysfunction (Naismith *et al.* 2012) pointing to the possibility of shared mechanisms with BP and its variability. Principal among these comorbidities, periventricular and subcortical white matter lesions (WMLs) shown as hyperintensities [white matter hyperintensity (WMH)] on T2-weighted magnetic resonance imaging (MRI) is considered the hallmark feature of vascular LOD (Sneed *et al.* 2008; Taylor *et al.* 2013). The progression of CVD and WMLs are closely related to systolic BP (Qiu *et al.* 2005; Tzourio *et al.* 2014) and BPV (Havlik *et al.* 2002; Gunstad *et al.* 2005; Brickman *et al.* 2010), highlighting BPV as a plausible mechanism impinging on cerebrovascular integrity. Specifically, systolic BPV has been linked with global cognitive performance (Nagai *et al.* 2012; Sabayan *et al.* 2013; Conway *et al.* 2015), psychomotor speed and executive function (Yano *et al.* 2014). These emerging findings parallel the cognitive deficits observed in

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vascular LOD (Pimontel *et al.* 2013) from disrupted fronto-striatal circuits (Taylor *et al.* 2013). Executive dysfunction in LOD might clinically present as difficulties with psychomotor speed and verbal fluency (Alexopoulos 2001). Thus the affected and spared cognitive domains, and cerebral regions, documented in vascular LOD coalesce with the emerging BPV-cognition literature.

The current study extends beyond previous reports by examining BPV in relation to depression and cognitive decline in a prospective cohort of elderly individuals who underwent serial neurological, BP and depression assessments over a 10-year period. We hypothesized that systolic BPV would be significantly associated with LOD but not early onset depression (EOD) or no depression disorder. Secondly, we hypothesized that the interaction between systolic BPV and LOD would be associated with accelerated decline in verbal fluency, psychomotor speed, and executive function over time. In a MRI substudy, we investigated the association between BPV with cognitive decline taking baseline WMH volumes into consideration. We hypothesized that the interaction between BPV with depression and WMH volume would be significantly associated with cognitive decline, and this would be evident with deep WMH more so than periventricular WMH (Sneed *et al.* 2008).

Methods and materials

Population

The Three-City (3C) Study is a French prospective cohort study investigating the determinants of dementia, CVD and stroke as reported previously (The 3C Study Group, 2003; Alpérovitch *et al.* 2015; Torres *et al.* 2015). Briefly, 9294 non-institutionalized community dwelling adults aged 65 years or older were sampled from the electoral rolls of Dijon, Bordeaux and Montpellier cities. The current analyses use only participants from Dijon because this site utilized the same cognitive tests across study waves and included a MRI substudy. Participants underwent baseline neurological examinations and serial follow-up was scheduled approximately 2, 4, 7, and 10 years later. Participants from Dijon were eligible for the current study if they did not have dementia or stroke at baseline and completed at least the 4-year follow-up when depression disorders were reassessed, and to provide a sufficient number of clinic visits for estimating BPV (Tully *et al.* 2016*a*). Persons who developed incident stroke over follow-up were also excluded from the main analysis ($n = 58$) because clinical strokes abruptly affect cognitive function and may result in lower BPV. Differences between the participating recruitment sites and the excluded participants are reported in the eSupplement. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and each participant provided signed and informed consent.

Primary exposure: BPV

Clinic BP was measured according to a standardized protocol as previously reported (Brindel *et al.* 2006). Clinic BP was measured three times, separated by 2 min after the subject rested at least 5 min in a seated position. An appropriately sized cuff was placed on the left arm and BP was measured using a validated digital electronic tensiometer OMRON M4 (OMRON Corp., Kyoto, Japan). Three measures were taken at each clinic visit in the first 4 years (up to a maximum of 9 BP readings from baseline, year 2 and year 4). We utilized the coefficient of variation (CV) method to calculate BPV between baseline and year 4 (eSupplement) because of the prognostic association with cerebrovascular outcomes (Tai *et al.* 2015) and its recommended use when estimating longer-term BPV (Parati *et al.* 2013). Systolic and diastolic BPV values were log transformed.

Assessment of depression and depressive symptoms

For depression assessment participants underwent face-to-face interviews with trained clinical psychologists. The MINI International Neuropsychiatric Interview (MINI) (Sheehan *et al.* 1998) was used at baseline, 4, 7 and 10-year follow-up. The MINI has established psychometric validity for affective disorders including inter-rater agreement and concurrent validity with other structured clinical interviews (Lecrubier *et al.* 1997). The current study utilized only the major depression and dysthymia MINI modules. Age of depression onset was determined at interview by asking participants the age of onset of their first depression episode, age of onset of the most recent depression episode (if not current), and age of onset of the current depression episode. Ages of 50, 60, and 65 years have been commonly used to determine age of onset (Naismith *et al.* 2012) and we dichotomized LOD age of onset at age 60 years or older (Tully *et al.* 2016*c*). Thus, any major depression or dysthymia disorder identified at baseline or during follow-up with an age of onset $\geqslant$60 years was categorized as LOD. Onset age 59 or younger was categorized as EOD. No other clinical data were available regarding lifetime depression, psychiatric history, or inpatient records. Symptomatic depression was assessed at baseline and every follow-up with the Centre for Epidemiological Studies-Depression (CESD) scale and scores $\geqslant$16 are indicative of clinically relevant depressive symptoms (Radloff, 1977). Participants were stratified based on depressive disorder and having two or more CESD measures in the symptomatic range (total score $\geqslant$16). Participants were stratified into one of six groups (dummy coded) based on depressive disorder and having two or more CESD measures in the symptomatic range (total score $\geqslant$16). The categories were; LOD-symptomatic, EOD-symptomatic, no depression disorder-symptomatic, LOD-asymptomatic, EOD-asymptomatic, no depression disorder history, and asymptomatic (reference). The rationale was to discriminate between persons with symptomatic depression, asymptomatic depression, and also account for the duration of depressive illness and severity because individuals with persistent depressive symptoms exhibit more rapid deterioration in brain function and pathology (Riddle *et al.* in press).

Assessment of cognitive function

Participants underwent assessments with a battery of validated cognitive tests administered by trained clinical psychologists. The Trail Making Test (TMT) (Armitage, 1946) is a test of visual attention, processing speed, mental flexibility, and broadly representative of executive function. The ratio of time to complete section B divided by the time to complete section A was used as the performance measure because this is shown to measure executive function independent of processing speed and working memory (Sanchez-Cubillo *et al.* 2009). TMT scores were multiplied by -1, so that negative β values signify worse performance. Isaac's Set Test (IST) evaluates verbal fluency abilities and speed of verbal production (Isaacs & Kennie, 1973). Respondents have to give a

https://doi.org/10.1017/S0033291717002756 Published online by Cambridge University Press

list of words belonging to a specific semantic category in 30 s. Four semantic categories were successively used (cities, fruits, animals, and colors). The Benton Visual Retention Test (BVRT) evaluates immediate visual recognition memory and attention (Benton, 1945). After the presentation for 10 s of a stimulus card displaying a geometric figure, respondents are asked to choose the initial figure among four possibilities; 15 figures are successively presented. The Mini Mental State Examination (MMSE) tests global cognitive function (Folstein *et al.* 1975). The Finger Tapping Test (FTT) is a test of psychomotor speed and manual dexterity. Participants completed two trials each of 60 s duration with their dominant and non-dominant hand (four trials in total). The average number of taps was the performance measure. TMT was not assessed at the 2-year follow-up, and FTT was only assessed at the 7- and 10-year follow-up. All other tests were completed at baseline and each wave of follow-up. Diagnoses of dementia was made by local neurologists according to DSM-IV criteria and then adjudicated by a panel of independent neurology experts (The 3C Study Group, 2003).

MRI scans

The parameters of the MRI examination in 3C were reported previously (The 3C Study Group, 2003) and described more fully in the eSupplement. The MRI evaluation of WMH excluded participants with brain tumor and unknown stroke history. All brain scans were acquired using the same MRI machine (1.5 T; Siemens, Erlangen) and the same standardized image acquisition protocol. First, a three-dimensional (3D) high-resolution T1-weighted brain volume was acquired using a 3D inversion recovery fast spoiled-gradient echo sequence (3D SPGR; TR, 9.7 ms; TE, 4 ms; TI, 600 ms; coronal acquisition). The axially reoriented 3D volume matrix size was $256 \times 192 \times 256$, with a voxel size of $1.0 \times 0.98 \times 0.98$ mm^3. Second, T2-weighted brain volumes were acquired using the same 2D fast spin-echo sequence with two echo times (TR: 4400 ms; TE1: 16 ms; TE2: 98 ms). T2 acquisition consisted of 35 3.5-mm-thick axial slices (with 0.5-mm spacing between slices), having a matrix size of 256×256, and an in-plane resolution of 0.98×0.98 mm^2.

Details of WMH estimation is described more fully elsewhere (Maillard *et al.* 2008). Fully automatic image processing software was developed to detect, measure, and localize WML using multispectral (T1, T2, PD) segmentation and identifying different classes of WMH voxels. Definitions of the region of interest are provided in the eSupplement. Some false positives corresponded to voxels that were white matter but not hyperintensities, i.e. voxels with a very low intensity but a higher probability of belonging to the WMH than to the white matter category (this may occur because the variance of WMH voxels is larger than that of white matter). Consequently, WMH with a mean T2 signal intensity below that of white matter were excluded.

WML load was expressed as the total volume of WML normalized by the volume of the WM mask, which accounts for both head size and for the T2 image acquisition actual field of view. WMH were classified according to distance to the ventricle as periventricular (<10 mm) or deep, and we did not differentiate juxtaventricular WMH. Periventricular WMH volume and deep WMH volume were estimated by adding up the volumes of all hyperintensities detected in each of these areas. WML volume was log-transformed [natural log of (volume in mL + 1)]. The quantification of WMLs was compared and validated against a neurologist visual rating blinded to covariates (Maillard *et al.* 2008) using a modified version of the Scheltens scale (Scheltens *et al.* 1992), which provides an overall WMH grade; none, mild, moderate, and severe. Parallel imaging and fluid-attenuation inversion recovery (FLAIR) sequences were not acquired in the 3C study.

Assessment of covariates

Reported in the eSupplement.

Statistical analyses

Descriptive comparisons utilized the general linear model, Kruskal–Wallis test, and Mantel–Haenszel test. The first set of analyses established whether BPV was associated with specific depression subtypes. BPV was modeled with curve fitting and maximum-likelihood estimation, which showed that a linear normal-identity distribution provided the most appropriate fit. Two sets of regressions were run to establish the association between BPV and the onset of depression, utilizing independent variables, (1) EOD and LOD (*v.* no depression), and (2) symptomatic *v.* asymptomatic LOD and EOD (*v.* no depression). The regressions entered the depression categories described above into the model with age, sex, education, and mean systolic BP. In the second step, covariates were added; antihypertensive drug use for hypertension, coronary heart disease, arrhythmia, chronic kidney disease (CKD), diabetes, body mass index (BMI), hypercholesterolemia, smoking status, alcohol intake, coffee consumption, apolipoprotein E $\varepsilon 4$ allele (APOE), and psychotropic drug use. These analyses were performed separately for systolic and diastolic BPV.

The relationship between BPV and depression with cognitive decline in each cognitive test was assessed with linear mixed models to estimate within and between subject effects and change over time. As other authors note, mixed models has several advantages for repeated measurements on the same individual are performed including great flexibility to model time effects, and adequately handle missing data (Marijnissen *et al.* 2017). The mixed models specified correlated residuals within subjects and random effects with restricted maximum likelihood function and robust covariance estimation. The data analysis assessed the slope of cognitive function over time, utilizing a random slope and random intercept. In the first instance, we stratified by symptomatic depression and tested interaction terms between time with depression groups and BPV. Separate models were run for systolic and diastolic BPV. All mixed models were adjusted for the abovementioned covariates. A sensitivity analysis was also performed for systolic BPV excluding persons who developed dementia during follow-up to remove any floor-effects in the cognitive tests.

In the MRI substudy, we examined change in cognitive function using repeated measures analysis of variance (ANOVA), adjusted for age, sex, education, APOE, and mean systolic BP. Because of the smaller MRI dataset we were only able to stratify the analyses by depression disorder (LOD, EOD, no disorder) and by symptomatic status over follow-up (symptomatic or asymptomatic on CESD) in two separate analyses. We entered main and interaction effects for time, depression, systolic BPV, and WMH volume. A set of ancillary analyses assessed these main and interaction effects according to deep and periventricular WMH volumes to identify whether WMH in specific brain locations was associated with cognitive decline. All analyses were

https://doi.org/10.1017/S0033291717002756 Published online by Cambridge University Press

Table 1. Characteristics of study participants according to depression status (N = 2812)

	Late onset depression		Early onset depression		No depression disorder		*p*
	Symptomatic *N* = 105	Asymptomatic *N* = 200	Symptomatic *N* = 51	Asymptomatic *N* = 74	Symptomatic *N* = 190	Asymptomatic *N* = 2192	
Female sex	81 (77.1)	167 (83.5)	40 (78.4)	58 (78.4)	113 (59.5)	1329 (60.6)	0.001
Age in years, median (IQR)	72.0 (69.5–76.0)	72.0 (68.0–76.0)	73.0 (69.0–77.0)	72.0 (69.0–76.3)	74.0 (70.0–78.0)	72.0 (69.0–76.0)	0.004
Primary education	31 (29.5)	35 (17.5)	15 (29.4)	11 (14.9)	50 (26.3)	396 (18.1)	<0.001
Short secondary schooling	49 (46.7)	100 (50.0)	23 (45.1)	34 (45.9)	75 (39.5)	942 (43.0)	
Full secondary schooling	15 (14.3)	35 (17.5)	10 (19.6)	14 (18.9)	31 (16.3)	429 (19.6)	
Higher education/degree	10 (9.5)	30 (15.0)	3 (5.9)	15 (20.3)	34 (17.9)	425 (19.4)	
Psychotropic drug use	49 (46.7)	70 (35.0)	34 (66.70)	32 (43.2)	78 (41.1)	393 (17.9)	<0.001
Anti-hypertensive drug use	49 (46.7)	90 (45.0)	31 (60.8)	31 (41.9)	103 (54.2)	994 (45.3)	0.01
Systolic BP, M ± S.D.	139.9 ± 19.4	138.8 ± 16.8	138.5 ± 16.0	139.5 ± 16.7	140.7 ± 14.8	143.4 ± 16.7	<0.001
Diastolic BP, M ± S.D.	78.0 ± 8.9	78.3 ± 8.5	77.3 ± 7.6	77.6 ± 8.5	78.9 ± 8.4	79.1 ± 8.6	0.16
CV systolic BP, median (IQR)	11.3 (8.5–14.7)	9.4 (6.1–13.3)	10.3 (7.5–13.1)	9.6 (6.9–11.5)	9.4 (6.8–12.7)	8.9 (6.1–12.3)	0.003
CV diastolic BP, median (IQR)	10.1 (7.2–15.7)	8.9 (6.1–12.0)	9.2 (5.9–12.4)	8.6 (6.5–12.3)	9.1 (6.2–12.9)	9.1 (6.2–12.6)	0.55
Coronary heart disease	26 (24.8)	41 (20.5)	19 (37.3)	11 (14.9)	60 (31.6)	488 (22.3)	0.002
Arrhythmia	28 (26.7)	33 (16.5)	23 (45.1)	15 (20.3)	41 (21.6)	460 (21.0)	0.14
Hypercholesterolemia	43 (41.0)	82 (41.0)	26 (51.0)	27 (36.5)	84 (44.2)	826 (37.7)	0.024
Diabetes	14 (13.3)	18 (9.0)	5 (9.8)	4 (5.4)	21 (11.1)	230 (10.5)	0.83
Chronic kidney disease	21 (20.0)	43 (21.5)	11 (21.6)	13 (17.6)	32 (16.8)	380 (17.3)	0.058
Apolipoprotein E ε4 allele	21 (20.6)	35 (17.8)	9 (18.4)	14 (20.0)	37 (20.6)	437 (20.4)	0.76
Body mass index, median (IQR)	25.6 (23.5–29.1)	25.2 (22.8–27.9)	25.3 (22.4–29.1)	24.5 (23.0–26.6)	25.2 (22.8–28.1)	25.3 (23.1–27.8)	0.31
Alcohol intake p/day in g, median (IQR)	2.7 (0–9.8)	6.9 (0–11.0)	3.1 (0–11.3)	8.9 (0–12.3)	9.6 (1.1–20.6)	9.6 (1.4–19.2)	<0.001
Tobacco smoking, former smoker	24 (22.9)	48 (24.0)	13 (25.5)	19 (25.7)	67 (35.3)	716 (32.7)	0.27
Current smoker	7 (6.7)	9 (4.5)	2 (3.9)	1 (1.4)	9 (4.7)	115 (5.2)	
Coffee intake cups p/day, median (IQR)	1.0 (0–2.0)	2.0 (1.0–2.0)	2.0 (0–3.0)	1.0 (0–2.0)	1.0 (0.3–2.0)	2.0 (1.0–2.0)	0.020

BP, blood pressure; CV, coefficient of variation; IQR, interquartile range.
Early onset depression, onset age <60 years.
Late onset depression, onset age >60 years.
Symptomatic depression determined as Centre for Epidemiological Studies-Depression scale scores ⩾ 16 on 2 or more assessments.

performed with PASW for Windows® version 22.0, a p value ⩽0.05 was considered as statistically significant.

Results

The final sample includes 2812 participants with a median age of 72 years [interquartile range (IQR) 69–76] and was comprised 63.6% females. Classification by depression onset and CESD scores was; 3.7% LOD-symptomatic, 7.1% LOD-asymptomatic, 1.8% EOD-symptomatic, 2.6% EOD-asymptomatic, 6.8% no depression disorder-symptomatic, and 78% no depression disorder-asymptomatic (Table 1). There were differences between depression groups on key variables including median age, sex, education, psychotropic and antihypertensive drug use, systolic and diastolic BP, systolic BPV, coronary heart disease, hypercholesterolemia, alcohol intake, and coffee consumption.

Association between BPV and depression onset

The regressions reporting the association between systolic BPV and depression groups are reported in (Table 2). Mean BPV by depression group is shown in eFig. 2. Higher systolic BPV was significantly associated with LOD after adjustment for covariates ($\beta = 0.83$, $p = 0.03$). Further stratification of LOD and EOD by symptomatic depression on the CESD indicated that systolic BPV was associated with symptomatic LOD ($\beta = 0.10$, $p = 0.037$) in fully adjusted analyses. Systolic BPV was associated with EOD-symptomatic ($\beta = 0.15$, $p = 0.024$) and LOD-asymptomatic ($\beta = 0.09$, $p = 0.015$) in analyses adjusted for age, sex, education and mean systolic BP but not fully adjusted models. Depression groups were not significantly associated with higher diastolic BPV (eSupplement Table 1).

Longitudinal association between BPV and depression with cognitive function

Raw cognitive test scores at baseline are provided in the eSupplement Table 2. The results of the mixed model analyses utilizing systolic BPV are reported in Fig. 1. The interaction between systolic BPV, LOD-symptomatic and time was generally associated with cognitive decline. The systolic BPV, LOD-symptomatic and time interaction was associated with verbal fluency (IST: $p = 0.040$), immediate visual memory (BVRT: $p = 0.049$), general cognitive function (MMSE: $p = 0.007$), and psychomotor function (FTT: $p = 0.017$). The main and interaction terms for systolic BPV, LOD-symptomatic and time was not significant for processing speed (TMTA: $p = 0.79$) or executive function (TMTB/A: $p = 0.23$).

The diastolic BPV, depression and time interaction terms were not significant and thus excluded from the final diastolic BPV models (eSupplement Table 3). The mixed model analyses of diastolic BPV showed that LOD-symptomatic was associated with verbal fluency (IST: $p = 0.029$) and immediate visual memory (BVRT: $p = 0.041$). Diastolic BPV was associated with visual memory (BVRT: $p = 0.001$), general cognitive function (MMSE: $p = 0.039$), and processing speed (TMTA: $p = 0.014$). Notably, mean systolic and diastolic BP were not significantly associated with cognitive decline in the mixed models.

The sensitivity analysis excluding persons who developed dementia generally corroborated the above findings. The systolic BPV, LOD-symptomatic, and time interaction were associated with verbal fluency [IST: $\beta = -6.15$, 95% confidence interval (CI) −10.61 to −1.69, $p = 0.007$], immediate visual memory (BVRT: $\beta = -1.13$, 95% CI −2.11 to −0.15, $p = 0.024$), general cognitive function (MMSE: $\beta = -1.05$, 95% CI −2.01 to −0.08, $p = 0.034$), psychomotor function (FTT: $\beta = -8.18$, 95% CI

Table 2. Association between depression and systolic blood pressure variability over 10 years (N = 2812)

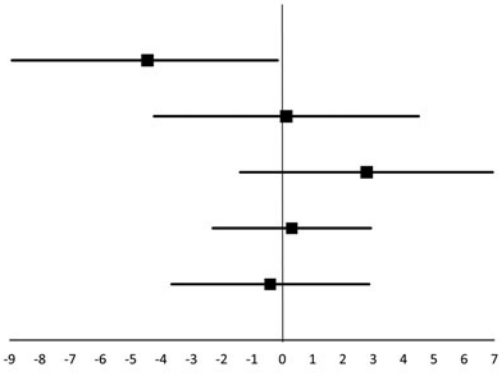
	Step 1 Age, sex, education and mean systolic BP adjusted			Step 2 + additional covariates		
	β	S.E.	p	β	S.E.	p
Depression disorder onset						
Late onset depression (LOD), onset age >60 years	1.06	0.38	0.006	0.83	0.38	0.030
Early onset depression, onset age <60 years	0.52	0.46	0.26	0.09	0.46	0.85
No depression disorder	Ref	–	–	Ref	–	–
Symptomatic on CESD; ⩾2 or more assessments						
LOD	0.12	0.05	0.010	0.10	0.05	0.037
Early onset depression	0.15	0.07	0.024	0.09	0.07	0.18
No depression disorder	0.05	0.04	0.22	0.03	0.04	0.47
Asymptomatic on CESD; ⩽1 or less assessments						
LOD	0.09	0.04	0.015	0.07	0.04	0.067
Early onset depression	0.02	0.05	0.97	−0.01	0.05	0.90
No depression disorder	Ref	–	–	Ref	–	–

APOE, apolipoprotein E ε4 allele; BMI, body mass index; BP, blood pressure; CESD, Center for Epidemiologic Studies Depression Scale; CHD, coronary heart disease; CKD, chronic kidney disease; S.E., standard error.
Step 1 adjusted for age, sex, education and mean systolic blood pressure.
Step 2 additionally adjusted for antihypertensive drug use for hypertension, CHD, arrhythmia, CKD, diabetes, BMI, hypercholesterolemia, smoking status, alcohol intake, coffee consumption, APOE, cancer, and psychotropic drugs.

https://doi.org/10.1017/S0033291717002756 Published online by Cambridge University Press

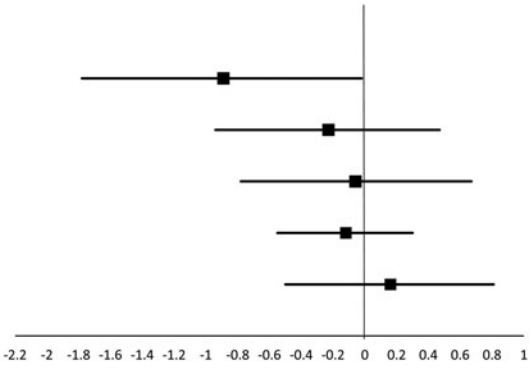
(*a*)

CESD ≥ 16	Interaction	β	95% CI	P
≥ 2 times	Time * LOD * Systolic BPV	-4.45	-8.92 to -.16	.04
	Time * EOD * Systolic BPV	.13	-4.23 to 4.50	.95
	Time * No disorder * Systolic BPV	2.78	-1.39 to 6.94	.19
≤ 1 time	Time * LOD * Systolic BPV	.31	-2.29 to 2.92	.81
	Time * EOD * Systolic BPV	-3.65	.40 to 2.86	.81



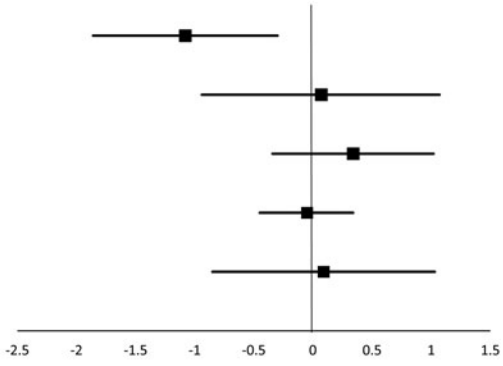
(*b*)

CESD ≥ 16	Interaction	β	95% CI	P
≥ 2 times	Time * LOD * Systolic BPV	-.89	-1.77 to -.01	.049
	Time * EOD * Systolic BPV	-.23	-.94 to .47	.52
	Time * No disorder * Systolic BPV	-.06	-.78 to .66	.87
≤ 1 time	Time * LOD * Systolic BPV	-.12	-.55 to .30	.57
	Time * EOD * Systolic BPV	.16	-.50 to .81	.64



(*c*)

CESD ≥ 16	Interaction	β	95% CI	P
≥ 2 times	Time * LOD * Systolic BPV	-1.08	-1.86 to -.30	.007
	Time * EOD * Systolic BPV	.07	-.94 to 1.07	.90
	Time * No disorder * Systolic BPV	.34	-.34 to 1.02	.33
≤ 1 time	Time * LOD * Systolic BPV	-.05	-.45 to .34	.80
	Time * EOD * Systolic BPV	.09	-.85 to 1.03	.85



(*d*)

CESD ≥ 16	Interaction	β	95% CI	P
≥ 2 times	Time * LOD * Systolic BPV	-7.53	-13.71 to -1.34	.017
	Time * EOD * Systolic BPV	20.24	-21.48 to 61.95	.34
	Time * No disorder * Systolic BPV	9.36	-9.22 to 27.93	.32
≤ 1 time	Time * LOD * Systolic BPV	-.37	-3.36 to 2.63	.81
	Time * EOD * Systolic BPV	1.75	-4.46 to 7.96	.58

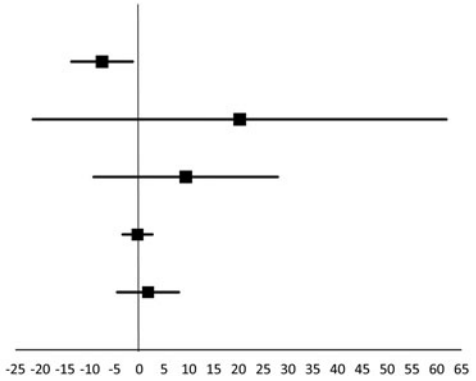


Fig. 1. Forest plots showing the β and 95% CI for cognitive decline (slope) in mixed models entering depression, systolic BPV and their interaction terms. BPV, blood pressure variability; CI, confidence interval; EOD, early onset depression; LOD, late onset depression; (*a*) IST, Isaac's Set Test; (*b*) BVRT, Benton Visual Retention Test; (*c*) MMSE, Mini Mental State Examination; (*d*) FTT, finger tapping test; (*e*) TMT-A, Trail Making Test-Part A multiplied by negative 1; (*f*) TMT B/A, ratio of time to complete Trail Making Test Part B divided by time to complete Trail Making Test Part A multiplied by negative 1.

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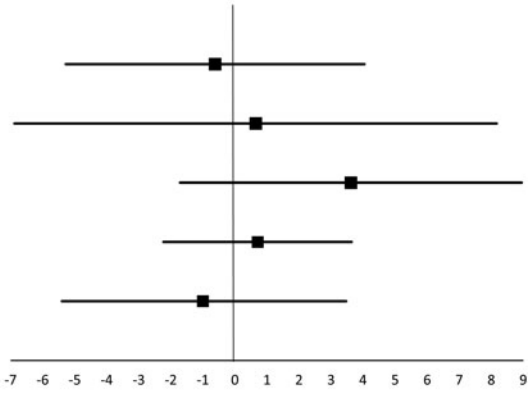
(*e*)

CESD ≥ 16	Interaction	β	95% CI	P
≥ 2 times	Time * LOD * Systolic BPV	.62	-5.28 to 4.04	.79
	Time * EOD * Systolic BPV	.65	-6.87 to 8.17	.87
	Time * No disorder * Systolic BPV	3.62	-1.71 to 8.95	.18
≤ 1 time	Time * LOD * Systolic BPV	.71	-2.23 to 3.64	.64
	Time * EOD * Systolic BPV	-.97	-5.40 to 3.47	.67



(*f*)

CESD ≥ 16	Interaction	β	95% CI	P
≥ 2 times	Time * LOD * Systolic BPV	-.19	-.50 to .12	.23
	Time * EOD * Systolic BPV	.05	-.30 to .40	.78
	Time * No disorder * Systolic BPV	.15	-.10 to .40	.23
≤ 1 time	Time * LOD * Systolic BPV	.05	-.10 to .21	.51
	Time * EOD * Systolic BPV	.18	-.08 to .44	.18

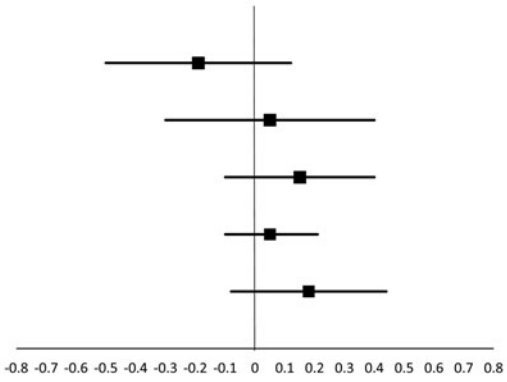


Fig. 1. (Continued).

−15.41 to −0.94, $p = 0.027$), processing speed (TMTA: $\beta = -1.05$, 95% CI −2.01 to −0.08, $p = 0.034$) but not executive function (TMTB/A: $\beta = -8.03$, 95% CI −16.79 to 0.72, $p = 0.072$).

MRI substudy

In the MRI substudy, repeated-measures ANOVA analyses showed several interaction effects between systolic BPV, depression and WMH. A scatterplot of WMH volumes and BPV is shown in eFigs 3 and 4. In analyses stratified by depression disorder (Fig. 2), verbal fluency was associated with a three-way time by systolic BPV by WMH volume interaction [IST: $F(3, 3642) = 5.56$, $p = 0.001$]. Immediate visual naming was associated with a three-way time by systolic BPV by depression disorder interaction [BVRT: $F(9, 3627) = 1.90$, $p = 0.049$]. General cognitive function was associated with systolic BPV by WMH volume interaction [MMSE: $F(1, 1221) = 4.27$, $p = 0.039$]. There were no main or interaction effects observed for TMTA, TMTB/A, or FTT. Analysis stratified by symptomatic depression provided the same interaction effects described above with the addition of a systolic BPV by symptomatic depression main effect for immediate visual naming [BVRT: $F(2, 1257) = 3.09$, $p = 0.046$].

Ancillary analysis

In the MRI substudy, all above interactions were reproduced when stratifying analysis by deep and periventricular WMH suggesting systolic BPV interactions were not specific to the location of WMH. Only general cognitive function was associated with periventricular WMH by systolic BPV interaction [MMSE: $F(1, 1221) = 5.07$, $p = 0.024$] and not deep WMH volume by systolic BPV interaction.

Discussion

This study adds to the extant literature by demonstrating a consistent association between systolic BPV with symptomatic depression and cognitive decline. Specifically, systolic BPV was associated with cognitive decline via interactions with symptomatic LOD in the main analysis. This association was evident for all cognitive measures apart from TMTA and TMTB/A, highlighting global cognitive function, visual memory, verbal fluency, and psychomotor speed as affected by systolic BPV and symptomatic LOD. By contrast, diastolic BPV was unrelated to depression, and less consistently associated with cognitive decline. The MRI substudy corroborated that systolic BPV was associated with cognitive decline via interactions with depression and WMH volume, both deep and periventricular.

Here we demonstrated that LOD was associated with higher systolic BPV supporting our first hypothesis. These findings extend the observation that depression disorder is associated with higher BPV over short periods (e.g. beat-to-beat) (Virtanen *et al.* 2003; Scuteri *et al.* 2009; Symonides *et al.* 2014), though no previous study discriminated between LOD and EOD. Our second hypothesis was also supported considering that the systolic BPV and symptomatic LOD interaction was associated with cognitive decline in verbal fluency, immediate visual memory, psychomotor speed and general cognitive function in the mixed models. Our findings parallel recent cross-sectional BPV studies showing that higher BPV is associated with psychomotor

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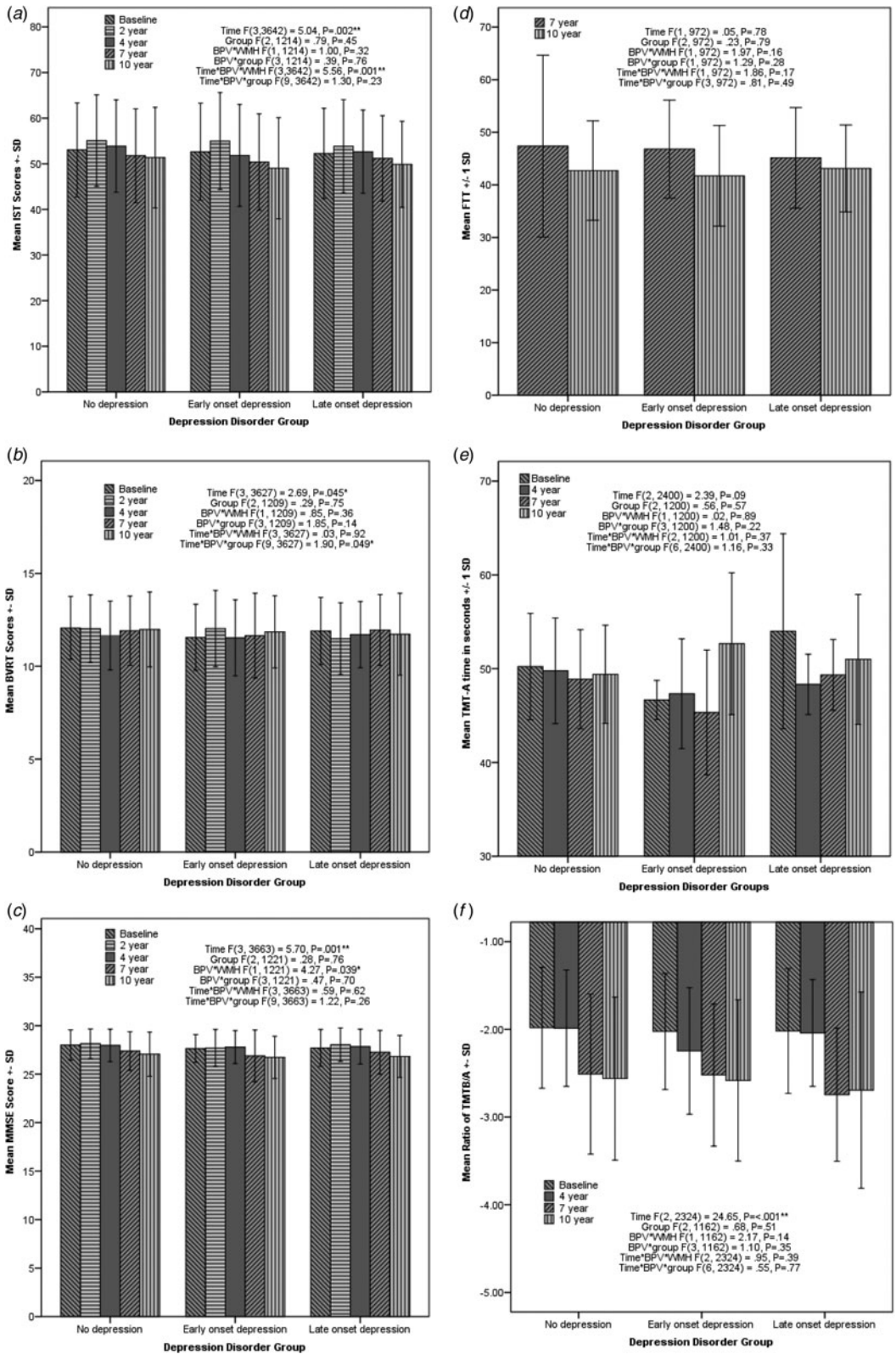

Fig. 2. Forest plots showing the mean and standard deviation for cognitive test scores in repeated measures ANOVA entering depression group, systolic BPV, white matter hyperintensity volume and their interaction terms. BPV, blood pressure variability; (*a*) IST, Isaac's Set Test; (*b*) BVRT, Benton Visual Retention Test; (*c*) MMSE, Mini Mental State Examination; (*d*) FTT, finger tapping test; (*e*) TMT-A, Trail Making TestPart A multiplied by negative 1; (*f*) TMT B/A, ratio of time to complete Trail Making Test Part B divided by time to complete Trail Making Test Part A multiplied by negative 1.

https://doi.org/10.1017/S0033291717002756 Published online by Cambridge University Press

speed and executive function (Yano *et al.* 2014) and global cognitive performance measured by the MMSE (Nagai *et al.* 2012; Sabayan *et al.* 2013; Conway *et al.* 2015). The MRI substudy corroborated that higher systolic BPV was associated with cognitive decline via interactions with WMH and symptomatic depression. The MRI substudy supports several large longitudinal studies on BPV and higher WMH volume (Havlik *et al.* 2002; Gunstad *et al.* 2005; Brickman *et al.* 2010). Our findings raise the possibility that cognitive decline is an expression of WMH potentiated by symptomatic depression and systolic BPV. Previously we showed that BPV increased the risk of dementia onset in this sample (Alperovitch *et al.* 2014) that was dependent on antihypertensive drug treatment with non-dihydropyridine calcium channel blockers and loop diuretics (Tully *et al.* 2016*a*).

The clinical implications of these findings closely relate to depression treatment augmentation with antihypertensive drugs that lower systolic BPV. A large meta-analysis demonstrated that BPV is lowered by calcium channel blockers and non-loop diuretics (Webb *et al.* 2010). This finding parallels clinical recommendations that augmentation of antidepressant regimen with calcium channel blockers was preferential in persons with LOD (Naismith *et al.* 2012). Supporting this recommendation, a study of fluoxetine augmentation with nimodipine (Taragano *et al.* 2005) showed significantly improved response on the Hamilton Depression Rating Scale and depression remission (Taragano *et al.* 2005). Otherwise, the role of calcium channel blockade has been predominantly implicated in bi-polar depression (Casamassima *et al.* 2010) and Alzheimer's disease (Amenta *et al.* 2008). It is less clear whether specific types of antihypertensive drugs can mitigate cognitive decline or progression to dementia (Tully *et al.* 2016*b*) especially in persons with WMH and concomitant LOD.

This study's strengths include a well defined cohort, comprehensive neurological and cognitive assessment over 10 years, serial BP assessment and use of a structured depression interview. Several limitations temper the conclusions drawn here including that we cannot infer causality between the observational measures and cognitive decline. Other limitations relate to the methodology including that the neuropsychological tests and the MINI were not performed at all follow-up points. Without comparison to normative data, it is difficult to ascertain the pattern and extent to which this sample has cognitive decline. Also, the cognitive test battery did not examine delayed-memory recall, a key cognitive domain that is impaired in Alzheimer's disease. As such, it is possible that persons with mild cognitive impairment and Alzheimer's disease were included in our sample at baseline and not identified by the neurologist panel. Moreover, persons with LOD are especially susceptible to dementia and extensive work indicates that hippocampal volume loss in LOD increases the risk for dementia (O'Brien *et al.* 1994; Hickie *et al.* 2005; Steffens *et al.* 2011; Jayaweera *et al.* 2016). Depression onset was determined at interview and would be unreliable in persons with memory impairments and is prone to retrospective reporting biases (Sneed *et al.* 2006). Also self-reports are less accurate than verified use of psychiatric treatments which could be garnered from psychiatric hospitalizations and outpatient data, which we did not utilize. A related point is that psychotropic drug use is higher in French samples compared with other European and North American samples. Specifically, a French national cohort study among 36 785 persons estimated anxiolytic use at 19.4%, antidepressants use at 11.6%, and hypnotic use at 9.2% (Grolleau *et al.* 2008). Another limitation is that we only quantified WMH volumes in a sub-sample of participants at baseline using 1.5 T MRI. A related point is that detection of WMH is commonly performed using FLAIR imaging, which we did not utilize in the 3C Dijon MRI study. Other limitations relate to the measurement of BP. The interval between BP assessments was 2–3 years, which may have less prognostic value than 24-h, diurnal and ambulatory BPV measures. Also, we utilized the CV method and other methodologies may produce different results. Finally, participants who were lost to follow-up were characterized by higher proportion of cardiovascular comorbidities such as arrhythmia that affect cognitive function (Taylor *et al.* 2006). Other important factors such as physical activity level, disability, sleep apnea, and predicted IQ are related to LOD and cognitive function and these were not assessed. As such, control for these important clinical factors would be important in future studies on LOD and cognitive function.

In conclusion, systolic BPV was associated with cognitive decline via interactions with symptomatic depression and WMH over a 10-year period in this elderly cohort. The collective findings support our hypothesis that systolic BPV increases cognitive decline via interactions with symptomatic depression and WMH. Future work might extend these findings by evaluating BPV prospectively with respect to incident 'vascular depression' and other depression subtypes.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717002756

Acknowledgements. The Three-City (3C) Study is conducted under a partnership agreement between the Institut National de la Sante et de la Recherche Medicale (INSERM), the Victor Segalen-Bordeaux II University, and Sanofi-Aventis. The Fondation pour la Recherche Medicale funded the preparation and initiation of the study. The Fondation Plan Alzheimer partly funded the follow-up of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salaries, Direction Generale de la Sante, MGEN, Institut de la Longevite, Conseils Regionaux of Aquitaine and Bourgogne, Fondation de France, la Caisse Nationale de Solidarité et d'Autonomie (CNSA) and the Ministry of Research-INSERM Programme 'Cohortes et collections de donnees biologiques'. The funding organizations played no role in the design and conduct of the study and were not involved in collection, management, analysis, and interpretation of the data or in preparation, review, or approval of the manuscript. The 3C Study supports are listed on the Study website (www.three-city-study.com).

Declaration of Interest. Dr Tully reports no biomedical financial interests or potential conflicts of interest. Professor Debette reports no biomedical financial interests or potential conflicts of interest. Professor Tzourio reports no biomedical financial interests or potential conflicts of interest.

References

Alexopoulos GS (2001) 'The depression-executive dysfunction syndrome of late life': a specific target for D3 agonists? *American Journal of Geriatric Psychiatry* **9**, 22–29.

Alperovitch A *et al.* (2014) Blood pressure variability and risk of dementia in an elderly cohort, the Three-City study. *Alzheimers and Dementia* **10**, S330–S337.

Alpérovitch A *et al.* (2015) Primary prevention with lipid lowering drugs and long term risk of vascular events in older people: population based cohort study. *British Medical Journal* **350**, h2335.

Amenta F *et al.* (2008) Nicardipine: a hypotensive dihydropyridine-type calcium antagonist with a peculiar cerebrovascular profile. *Clinical Experiments in Hypertension* **30**, 808–826.

Armitage SG (1946) An analysis of certain psychological tests used for the evaluation of brain injury. *Psychological Monographs* **60**, Whole No. 277, i–48.

Benton AL (1945) A visual retention test for clinical use. *Archives of Neurology and Psychiatry* **54**, 212–216.

Brickman AM *et al.* (2010) Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Archives of Neurology* **67**, 564–569.

Brindel P *et al.* (2006) Prevalence, awareness, treatment, and control of hypertension in the elderly: the Three City study. *Journal of Hypertension* **24**, 51–58.

Casamassima F *et al.* (2010) L-type calcium channels and psychiatric disorders: a brief review. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **153B**, 1373–1390.

Conway KS *et al.* (2015) Relationship between 24-hour ambulatory blood pressure and cognitive function in community-living older adults: the UCSD ambulatory blood pressure study. *American Journal of Hypertension* **28**, 1444–1452.

Dolan E and O'Brien E (2015) Is it daily, monthly, or yearly blood pressure variability that enhances cardiovascular risk? *Current Cardiology Reports* **17**, 93.

Folstein MF, Folstein SE and McHugh PR (1975) 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12**, 189–198.

Grolleau A *et al.* (2008) Psychotropic drug use and correspondence with psychiatric diagnoses in the mental health in the general population survey. *L'Encephale* **34**, 352–359.

Gunstad J *et al.* (2005) Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. *Blood Pressure* **14**, 353–358.

Havlik RJ *et al.* (2002) Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu-Asia Aging study. *Stroke* **33**, 26–30.

Hickie I *et al.* (2005) Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *The British Journal of Psychiatry* **186**, 197–202.

Isaacs B and Kennie AT (1973) The set test as an aid to the detection of dementia in old people. *The British Journal of Psychiatry* **123**, 467–470.

Jayaweera HK *et al.* (2016) Episodic memory in depression: the unique contribution of the anterior caudate and hippocampus. *Psychological Medicine* **46**, 2189–2199.

Lecrubier Y *et al.* (1997) The MINI international neuropsychiatric interview (M.I.N.I.) A short diagnostic structured interview: reliability and validity according to the CIDI. *European Psychiatry* **12**, 224–231.

Maillard P *et al.* (2008) An automated procedure for the assessment of white matter hyperintensities by multispectral (T1, T2, PD) MRI and an evaluation of its between-centre reproducibility based on two large community databases. *Neuroradiology* **50**, 31–42.

Marijnissen RM *et al.* (2017) Metabolic dysregulation and late-life depression: a prospective study. *Psychological Medicine* **47**, 1041–1052.

Nagai M *et al.* (2012) Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. *Journal of Hypertension* **30**, 1556–1563.

Naismith SL *et al.* (2012) The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. *Progress in Neurobiology* **98**, 99–143.

O'Brien JT *et al.* (1994) The differentiation of depression from dementia by temporal lobe magnetic resonance imaging. *Psychological Medicine* **24**, 633–640.

Parati G *et al.* (2013) Assessment and management of blood-pressure variability. *Nature Reviews Cardiology* **10**, 143–155.

Pimontel MA *et al.* (2013) The external validity of MRI-defined vascular depression. *The American Journal of Geriatric Psychiatry* **21**, S66–S67.

Qiu C, Winblad B and Fratiglioni L (2005) The age-dependent relation of blood pressure to cognitive function and dementia. *The Lancet Neurology* **4**, 487–499.

Radloff LS (1977) The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement* **1**, 385–401.

Riddle M *et al.* (in press) Longitudinal cognitive outcomes of clinical phenotypes of late-life depression. *The American Journal of Geriatric Psychiatry*.

Sabayan B *et al.* (2013) Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study. *British Medical Journal* **347**, f4600.

Sanchez-Cubillo I *et al.* (2009) Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society* **15**, 438–450.

Scheltens P *et al.* (1992) White matter lesions on magnetic resonance imaging in clinically diagnosed Alzheimer's disease. Evidence for heterogeneity. *Brain* **115**(Pt 3), 735–748.

Scuteri A *et al.* (2009) Decreased nocturnal systolic blood pressure fall in older subjects with depression. *Aging Clinical and Experimental Research* **21**, 292–297.

Sheehan DV *et al.* (1998) 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. *Journal of Clinical Psychiatry* **59**, 22–33.

Sneed JR *et al.* (2008) The vascular depression subtype: evidence of internal validity. *Biological Psychiatry* **64**, 491–497.

Sneed JR, Roose SP and Sackeim HA (2006) Vascular depression: a distinct diagnostic subtype? *Biological Psychiatry* **60**, 1295–1298.

Steffens DC *et al.* (2011) Change in hippocampal volume on magnetic resonance imaging and cognitive decline among older depressed and nondepressed subjects in the neurocognitive outcomes of depression in the elderly study. *American Journal of Geriatric Psychiatry* **19**, 4–12.

Symonides B *et al.* (2014) Does the control of negative emotions influence blood pressure control and its variability? *Blood Pressure* **23**, 323–329.

Tai C *et al.* (2015) Prognostic significance of visit-to-visit systolic blood pressure variability: a meta-analysis of 77,299 patients. *Journal of Clinical Hypertension* (*Greenwich*) **17**, 107–115.

Taragano FE, Bagnatti P and Allegri RF (2005) A double-blind, randomized clinical trial to assess the augmentation with nimodipine of antidepressant therapy in the treatment of 'vascular depression'. *International Psychogeriatrics* **17**, 487–498.

Taylor WD, Aizenstein HJ and Alexopoulos GS (2013) The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry* **18**, 963–974.

Taylor WD, Steffens DC and Krishnan KR (2006) Psychiatric disease in the twenty-first century: the case for subcortical ischemic depression. *Biological Psychiatry* **60**, 1299–1303.

The 3C Study Group (2003) Vascular factors and risk of dementia: design of the Three-City study and baseline characteristics of the study population. *Neuroepidemiology* **22**, 316–325.

Torres MJ *et al.* (2015) 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. *Osteoporosis International* **26**, 2157–2164.

Tully PJ *et al.* (2016a) Dementia risk with antihypertensive use and blood pressure variability: a cohort study. *Neurology* **87**, 601–608.

Tully PJ *et al.* (2016b) Diuretic antihypertensive drugs and incident dementia risk: a systematic review, meta-analysis and meta-regression of prospective studies. *Journal of Hypertension* **34**, 1027–1035.

Tully PJ *et al.* (2016c) The APOE epsilon 4 polymorphism does not predict late onset depression: the Three-City Study. *Neurobiology of Aging* **40**, 191.e199–191.e110.

Tzourio C, Laurent S and Debette S (2014) Is hypertension associated with an accelerated aging of the brain? *Hypertension* **63**, 894–903.

Virtanen R *et al.* (2003) Anxiety and hostility are associated with reduced baroreflex sensitivity and increased beat-to-beat blood pressure variability. *Psychosomatic Medicine* **65**, 751–756.

Webb AJ *et al.* (2010) Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *The Lancet* **375**, 906–915.

Yano Y *et al.* (2014) Long-term blood pressure variability throughout young adulthood and cognitive function in midlife: the coronary artery risk development in young adults (CARDIA) study. *Hypertension* **64**, 983–988.