

ORIGINAL ARTICLE

Excessive variability in systolic blood pressure that is self-measured at home exacerbates the progression of brain white matter lesions and cognitive impairment in the oldest old

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To investigate the effects of variability in self-measured systolic blood pressure at home on the progression of cognitive impairment and white matter lesions in the oldest old. Between April 2009 and October 2009, 248 oldest old aged 80 years or older were eligibly enrolled from geriatric practices and community-dwelling areas of Shandong, China. Self-measured blood pressure at home (HBP) was measured for 7 consecutive days at the baseline, and the Mini-Mental State Examination (MMSE) score and brain white matter hyperintensities (WMH) were assessed at the baseline and during the final follow-up visit. Variability in systolic HBP was evaluated using coefficient of variation (CV) in serial daily systolic HBP measurements of the last 6 consecutive days. After an average of 2.3 years of follow-up visits, 232 oldest old were included in and 16 were excluded from the analysis. The MMSE score declined -4.76 (interquartile ranges: $-10.71, -0.83$) %, the periventricular WMH, deep WMH, total WMH and WMH fraction increased 16.46 (s.d.: 6.72)%, 10.05 (s.d.: 6.40)%, 14.69 (s.d.: 6.07)% and 15.95 (s.d.: 6.32)%, respectively, in the total oldest old. A declined percentage of the MMSE score and increased percentages of the periventricular WMH, deep WMH, total WMH and WMH fraction in the high group divided by tertile of the CV of the systolic HBP at baseline were greater than those in the low group ($P < 0.05$). The significant differences were retained after adjusting for covariates, including the MMSE score, periventricular WMH, deep WMH and WMH fraction at the baseline ($P < 0.05$). Excessive variability in self-measured systolic HBP exacerbates the progression of cognitive impairment and brain white matter lesions in the oldest old.

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INTRODUCTION

The oldest old, aged 80 years or older,¹ is the fastest growing age group worldwide as life expectancy is steadily increasing. The risk of age-related diseases, such as cognitive impairment or dementia, develops at a higher rate and represents an important factor affecting the quality of life for the geriatric population.^{2,3} Epidemiological evidence^{1,4,5} demonstrated that cognitive impairment is common in elderly subjects, with more than half of this population showing signs of dementia.^{6–9} It is estimated that the prevalence of dementia is up to 24% in people aged 80–89 years and 37 percent in people aged 90 and older.^{1,5}

Brain white matter lesions (WMLs) are commonly observed on structural brain scans using MRI in aging individuals.^{10,11} White matter hyperintensities (WMHs) are pivotal indicators and one of the

pathological changes of WMLs.^{10,11} WMH emerges early in the presymptomatic phase, resulting in cognitive decline.^{10,12} Evidence has shown that increased WMH volume is closely associated with cognitive impairment and an increased risk of dementia.¹²

Alzheimer's disease is the most prevalent early and slow onset dementia in the elderly.¹³ Evidence has shown that the common presentation on an MRI of the brain is frontal and/or temporal brain atrophy changes, as well as white matter changes involving frontal and parietal structures in AD.¹⁴ Barnes *et al.*¹⁵ found that increased WMH is independently associated with longitudinal brain volume loss in subjects who lack clinically significant cognitive decline. In addition, older subjects who have an increased WMH burden are at higher risk for the development of AD.^{16–18}

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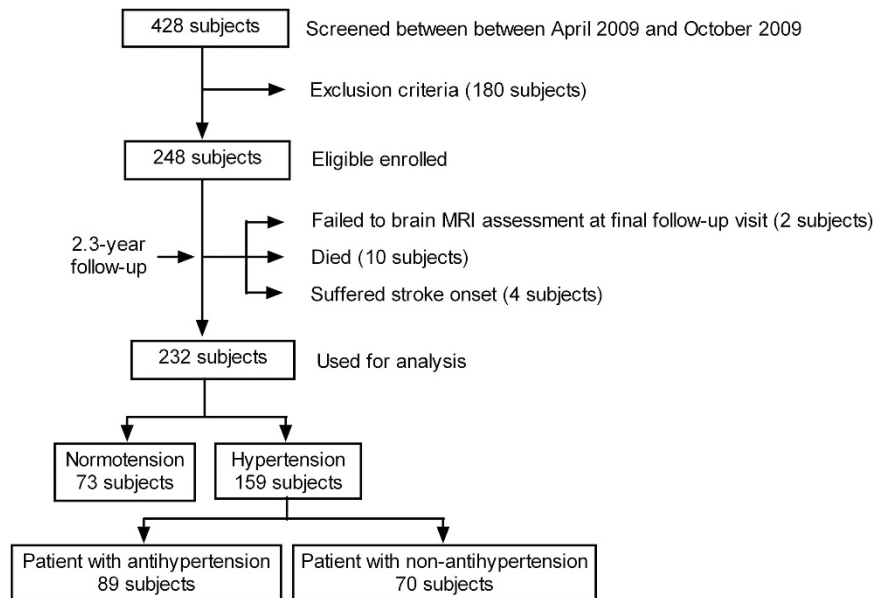


Figure 1 Flow diagram of the study.

More recently, self-measured blood pressure at home (home blood pressure, HBP) by patients is recommended by guidelines to evaluate the status of hypertensive patients.^{19,20} HBP monitoring provides multiple measurements of blood pressure over a much longer period and more accurately reflects an individual's blood pressure level, eliminates the white-coat and masked hypertension phenomena, overcomes some shortcomings of ambulatory blood pressure monitoring and avoids both observer and regression dilution biases.^{21–23} Importantly, it can provide information on the day-by-day variability in HBP under relatively well-controlled conditions.^{21–24}

The major goal of our study was to investigate the association of variability in systolic HBP with the progress of WMLs and cognitive impairment in the oldest old.

METHODS

Study population and design

This study was performed in compliance with the ethical standards established in the Declaration of Helsinki and was approved by the Research Ethics committee of Shandong Academy of Medical Sciences. All participants provided written informed consent.

This study was a longitudinal observational study. Between April 2009 and October 2009, a total of 428 oldest old with normotension or hypertension were screened from geriatric practices and community-dwelling in areas of Shandong, China. Of these participants, 248 were eligibly recruited for this study. The exclusion criteria included stroke, dementia, schizophrenia, seizures, Parkinson's disease, bipolar disorder, claustrophobia, secondary hypertension, end-stage heart disease, renal failure and dialysis treatment, diabetes mellitus, contraindication to MRI and inability with providing informed consent.

At baseline, each participant underwent a clinical visit to assess covariates, which included official blood pressure, history of hypertension, use of antihypertensive drugs, smoking, alcohol consumption, body mass index, education, blood lipid and glucose. Thereafter, a clinical visit was performed every 3 months. For the oldest old with hypertension, antihypertensive therapy had been advised by a cardiologist if the participant was willing to receive treatment. The antihypertensive agents included angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics or other medication. Because our study was an observational study, there was no unified antihypertensive schedule for participants with

Table 1 Characteristics and demographics of participants at baseline and final follow-up visit

	Baseline
Age, years	84.35 ± 2.52
Sex, F/M	173/59
Alcohol, units per week	0.41 ± 1.24
Smoker, n (%)	21 (9.05)
Education, years	6.72 ± 14.07
Body mass index, kg m ⁻²	23.49 ± 1.61
<i>Blood pressure</i>	
Official systolic blood pressure, mm Hg	150.54 ± 17.16
Official diastolic blood pressure, mm Hg	68.03 ± 7.35
Self-measured systolic blood pressure, mm Hg	146.25 ± 17.68
Self-measured diastolic blood pressure, mm Hg	64.67 ± 7.89
CV of self-measured systolic blood pressure, %	14.69 ± 7.00
CV of self-measured diastolic blood pressure, %	9.32 ± 5.06
<i>Biochemical examination</i>	
Total cholesterol, mmol l ⁻¹	4.47 ± 0.54
Triglycerides, mmol l ⁻¹	1.16 ± 0.45
High-density lipoprotein cholesterol, mmol l ⁻¹	1.32 ± 0.33
Low-density lipoprotein cholesterol, mmol l ⁻¹	2.62 ± 0.63
Fasting plasma glucose, mmol l ⁻¹	5.47 ± 0.42
<i>Cognitive function</i>	
Mini-mental state examination	25.00 (22.00, 26.00)
<i>Brain MRI</i>	
Periventricular white matter hyperintensity volume, ml	5.11 ± 2.90
Deep white matter hyperintensity volume, ml	1.77 ± 0.98
White matter hyperintensity volume, ml	6.88 ± 3.37
White matter hyperintensity volume fraction, %	0.49 ± 0.25
Antihypertension, n (%)	51 (21.98)

Abbreviations: CV, coefficient of variation; F, female; M, male. Results were represented as mean ± s.d.s or median with IQRs.

hypertension. HBP was measured at baseline, and cognitive function and WMH were assessed at baseline and during the final follow-up visit.

Self-measured HBP

HBP was measured as previously described.^{25,26} In brief, every eligible participant was supplied with an automatic device (BP3MX1-1, Microlife WatchBP Home), which was validated and satisfied the criteria of the European Society of Hypertension International Protocol.²⁷ After 5 min of sitting at rest and with a gap of 2 min between measurements, the HBP measurement was performed in the sitting position twice each morning (0600–0900 h) and twice each evening (1700–2100 h) for 7 consecutive days. The data were excluded

from the following analysis if any of the six consecutive HBP readings was invalidated.

HBP profiles were evaluated using the average of within-subject readings. Variability in systolic HBP was calculated as the coefficient of variation (CV) in serial daily systolic HBP measurements of the last 6 consecutive days. The CV was calculated as the following: $CV\% = \text{s.d. of the daily systolic HBP} / \text{average of the daily systolic HBP} \times 100$.

Assessment of MMSE

Assessment of global cognitive function was performed using the Mini-Mental State Examination (MMSE) by a neuropsychological expert who was blinded to

Table 2 Changes of MMSE score, periventricular WMH, deep WMH, total WMH and WMH fraction during follow-up period

	Total (n = 232)	Normotension (n = 73)	Hypertension (n = 159)	Antihypertension (n = 89)	Non-antihypertension (n = 70)
Change percentage of MMSE score, %	-4.76 (-10.71, -0.83)	-4.55 (-9.09, 0.00)	-7.41 (-11.11, -3.45)	-4.76 (10.81, 0.00)	-7.41 (-11.54, -3.70)*
Change percentage of PWMH, %	16.46 ± 6.72	16.11 ± 7.19	16.61 ± 6.51	15.49 ± 6.27	18.05 ± 6.59*
Change percentage of DWMH, %	10.05 ± 6.40	10.70 ± 6.59	9.75 ± 6.31	9.31 ± 6.60	10.32 ± 5.92
Change percentage of total WMH, %	14.69 ± 6.07	14.24 ± 6.43	14.90 ± 5.90	13.96 ± 5.82	16.10 ± 5.82*
Change percentage of WMH fraction, %	15.95 ± 6.32	15.46 ± 6.75	16.18 ± 6.11	15.24 ± 6.04	17.37 ± 6.04*

Abbreviations: DWMH, deep white matter hyperintensities; MMSE, Mini-Mental State Examination; PWMH, periventricular white matter hyperintensities; WMH, white matter hyperintensities. Results were represented as median with IQRs for change percentage of MMSE score, and mean ± s.d.s for change percentages of periventricular WMH, deep WMH, total WMH and WMH fraction. * $P < 0.05$, as compared with antihypertension.

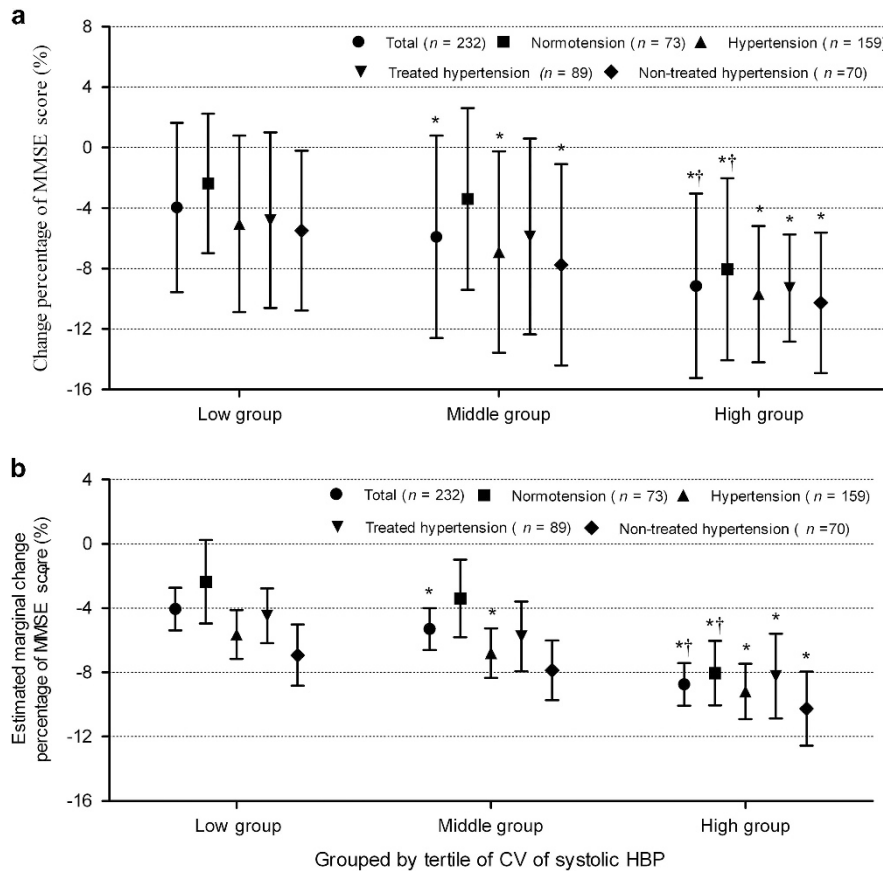


Figure 2 Effect of CV of systolic HBP on change percentage of the MMSE score during the follow-up period. (a) Shown as mean values with s.d.s. (b) Shown as estimated marginal mean values with 95% confidence intervals resulting from the analysis of covariance model adjusted for age, sex, the baseline body mass index, the baseline official blood pressure, the baseline blood lipid and glucose, education, smoking, alcohol consumption and the baseline MMSE score. MMSE indicates Mini-Mental State Examination. * $P < 0.05$, compared with the Low group; † $P < 0.05$, compared with the middle group.

the clinical and imaging outcomes of participants. The MMSE is a 30-point test that consists of five areas of potential cognitive impairment: orientation, registration, attention and calculation, and language. It is a validated and powerful tool for diagnosis in the advanced stages of cognitive impairment.

MRI scanning protocol and processing

Brain MRI acquisition was performed on the same 3 T GE Signa Horizon scanner (General Electric Medical Systems, Milwaukee, WI, USA) according to the same protocol. The sequences were used to image the brain as follows: a T1-weighted three-dimensional magnetization prepared rapid gradient echo sequence (isotropic 1-mm voxel, TR/TE/TI=1900/3/900 ms, flip angle 9°; acquisition matrix 256×256 with 160 slices yielding 1 mm³ isotropic voxels; field of view 256×240 mm², 1-mm thick slices, and no gap), T2-weighted three-dimensional fast spin-echo (TR/TE=3000/98 ms, field of view=24 cm, acquisition matrix=256×256, number of excitations=0.5, 3-mm slice thickness and no gap), and a fluid-attenuated inversion recovery (TR/TE/TI=5000/355/1800 ms, flip angle 120°, acquisition matrix 256×256 with 60 slices, 2-mm thick slices and no slice gap).

WMH volume was computed from an automated subcortical and periventricular segmentation routine with T2 scan using Freesurfer.²⁸ When the WMH was adjacent to a ventricle, the WMH was labeled as periventricular WMH; otherwise, it was deemed to be a deep WMH. The volumes of periventricular and deep WMH were calculated by summing the volumes of all of the hyperintensities detected in each area.²⁹ The total WMH=periventricular WMH+deep WMH. The TIV (total intracranial volume) was calculated as the sum of white matter, gray matter and cerebrospinal fluid volumes using

voxel-based morphometry techniques. The total volume of WMH was evaluated using a fraction of TIV as described by White:³⁰ WMH fraction (%)=(total WMH (ml)/TIV (ml))×100. Volumetric analysis of the WMLs was performed using the brain extraction tool (BET) and FMFIB's automated segmentation tool (FAST) tools from the FSL 4.1 software package.³¹ All MRI analyses were performed by the same neuro-radiologist who blinded to clinical, laboratory and cognitive function data.

Statistical analysis

Continuous data were presented as the mean±s.d., and categorical data were expressed as percentages. As the distribution was skewed, the MMSE scores were expressed as the median and interquartile range. Paired *t*-tests were performed to evaluate the differences of the characteristics of all participants between the baseline and final visits. Participants were classified into three groups: low, middle and high groups, according to the tertile of CV of systolic HBP at baseline. Change percentages were used and calculated as ((value at final—value at baseline)/value at baseline)×100. Differences in changes of the MMSE score, WMH and WMH fraction among strata in each group were assessed using one-way analysis of variance with Bonferroni procedure or Kruskal–Wallis test. The effect of CV of systolic HBP on change percentages of the MMSE score, WMH and WMH fraction were examined using a general linear model with multivariate analysis adjusted for covariates including the baseline MMSE score and baseline WMH fraction. Covariates included: age, sex, baseline body mass index, baseline official BP, baseline blood lipid and glucose, smoking and alcohol consumption. Statistical analysis was

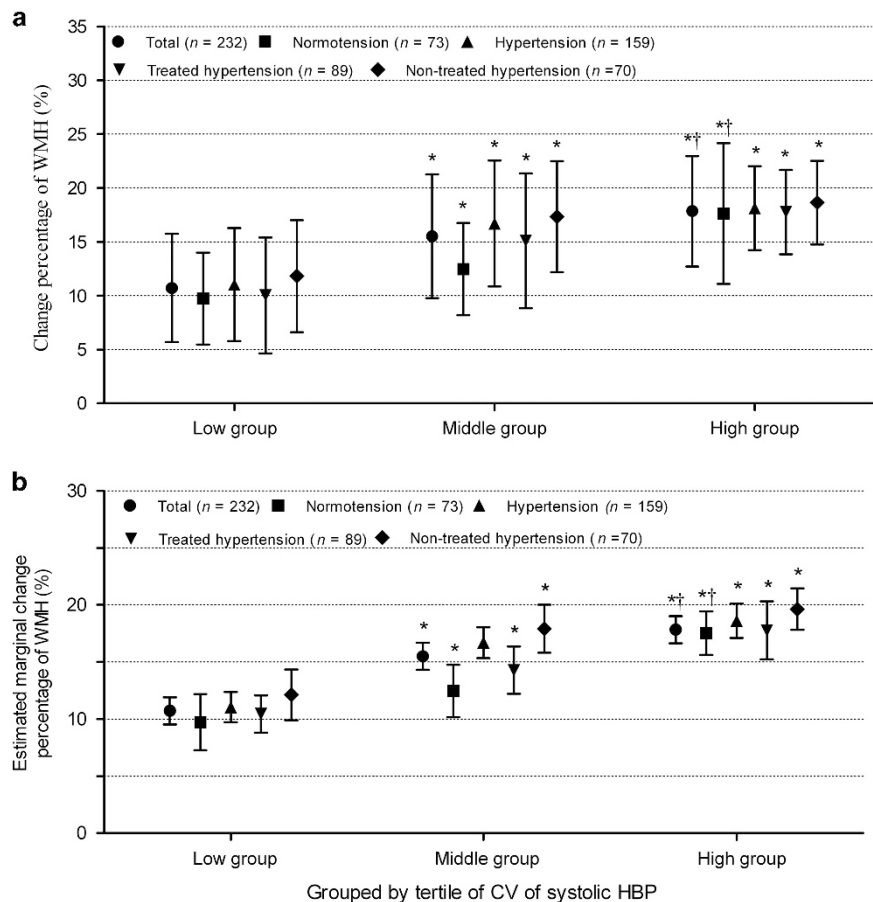


Figure 3 Effect of CV of systolic HBP on change percentage of white matter hyperintensities during the follow-up period. (a) Shown as mean values with s.d.s. (b) Shown as estimated marginal mean values with 95% confidence intervals resulting from the analysis of covariance model adjusted for age, sex, the baseline body mass index, the baseline official blood pressure, the baseline blood lipid and glucose, education, smoking, alcohol consumption and the baseline white matter hyperintensities fraction. WMH indicates white matter hyperintensities. **P*<0.05, compared with the Low group; †*P*<0.05, compared with the middle group.

performed using the SPSS for Windows software package, version 17.0 (SPSS, Chicago, IL, USA). A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Participants, demographic baselines and clinical characteristics

A flow diagram of the study is provided in Figure 1. Of the 248 participants, 16 were excluded for the following reasons: participants failed the brain MRI assessment during the final follow-up visit, 10 participants died and 4 participants suffered from stroke onset during an average follow-up period of 2.3 years. Finally, 232 participants completed the follow-up visit and were included in the analysis. Among these participants, 173 were females and were 59 males. There were 73 normotensives and 159 hypertensives participants. Among the hypertensive participants, 89 received antihypertensive treatment and 70 were free of antihypertensive treatment. The demographic baselines and clinical characteristics of the participants at baseline are represented in Table 1. Participants were followed for 2.3 (s.d.: 0.2) years on average. The CV of systolic HBP was $14.69 \pm 5.00\%$ and the tertile was $< 12.60\%$, $12.60\text{--}16.47\%$ and $> 16.47\%$.

Changes of MMSE score, periventricular WMH, deep WMH, total WMH and WMH fraction during the follow-up period

Changes in the MMSE score, periventricular WMH, deep WMH, total WMH and WMH fraction during the follow-up period are

shown in Table 2. The MMSE score declined, and the periventricular WMH, deep WMH, total WMH and WMH fraction increased in all normotensive participants over the 2.3 years of follow-up. Similar changes were also observed in hypertensive patients either with anti- or non-antihypertensive treatment. There were no significant differences in the change percentages of the MMSE score, periventricular WMH, deep WMH, total WMH and WMH fraction between normotensive and hypertensive participants. The MMSE score declined, and the periventricular WMH, total WMH and WMH fraction increased in non-antihypertensive patients and were significantly greater than antihypertensive patients ($P < 0.05$).

Effect of variability in systolic HBP on progression of cognitive impairment during the follow-up period

The effect of CV of systolic HBP on the change in the MMSE score during the follow-up period is shown in Figure 2. In all participants, there was an upward trend in the declined percentage of the MMSE score from the low to high group, and the differences were significant between any two groups even after adjusted for covariates, including the baseline MMSE score ($P < 0.05$). After adjusting for covariates, including the baseline MMSE score, declined percentages of the MMSE score in the high group were significantly greater compared with those in the low group in normotensive subjects and

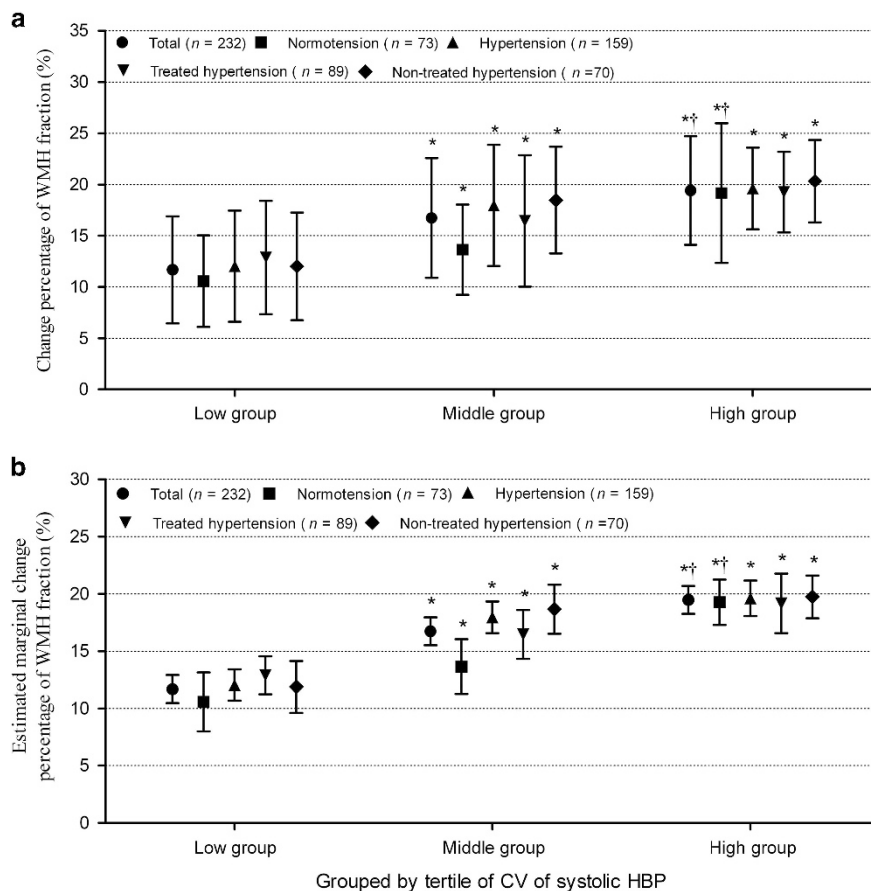


Figure 4 Effect of CV of systolic HBP on change percentage of white matter hyperintensities fraction during the follow-up period. (a) Shown as mean values with s.d.s. (b) Shown as estimated marginal mean values with 95% confidence intervals resulting from the analysis of covariance model adjusted for age, sex, the baseline body mass index, the baseline official blood pressure, the baseline blood lipid and glucose, education, smoking, alcohol consumption and the baseline white matter hyperintensities fraction. WMH indicates white matter hyperintensities. * $P < 0.05$, compared with the Low group; † $P < 0.05$, compared with the middle group.

hypertensive, antihypertensive and non-antihypertensive patients ($P < 0.05$, respectively).

Effect of variability in systolic HBP on progression of WMHs during the follow-up period

First, we determined the effect of CV of systolic HBP on the progression of total WMH and WMH fraction during the follow-up period. The change percentage of WMH is shown in Figure 3, and the change percentage of the WMH fraction is provided in Figure 4. In all participants and normotensive subjects, there was an upward trend in increased percentages of the WMH and WMH fraction from the low to high group, and the differences were significant between any two groups. After adjusting for covariates, which included the baseline WMH fraction, the trend and differences were maintained ($P < 0.05$, respectively). In hypertensive, antihypertensive and non-antihypertensive patients, increased percentages of WMH and WMH fraction in the middle and high groups were greater than those in the low groups after adjusting for covariates, including the baseline WMH fraction ($P < 0.05$, respectively).

Next, we evaluated the effect of CV of systolic HBP on the progression of periventricular WMH during the follow-up period (Figure 5). After adjusting for covariates, including baseline periventricular WMH, there was an upward trend in increased percentages of periventricular WMH from the low to high group, and these differences were significant between any two groups in total and antihypertensive subjects ($P < 0.05$, respectively). Increased

percentages of periventricular WMH in the high group were greater than that in the low and middle groups in normotensive subjects ($P < 0.05$). In hypertensive and non-antihypertensive patients, the increased percentages in the middle and high groups were higher than those in the low group after adjusting for covariates ($P < 0.05$).

Third, we assessed the effect of CV of systolic HBP on progression of deep WMH during the follow-up period (Figure 6). Covariates, including baseline deep WMH, were adjusted in all analyses. In all subjects, even patients who were classified into normotension, hypertension, antihypertension and non-hypertension groups, increased percentages of deep WMH in the high groups were greater compared with the low group ($P < 0.05$, respectively).

DISCUSSION

The main finding of the present study was that a higher CV of systolic HBP was associated with a declined percentage of the MMSE score and increased percentage of periventricular WMH, deep WMH, total WMH and WMH fraction during the follow-up period in normotensive subjects, hypertensive patients, antihypertensive patients and non-antihypertensive patients. These associations were independent of mean BP, antihypertensive treatment, the baseline MMSE score and baseline WMH and other confounding factors. Our findings indicated that excessive variability in systolic HBP exacerbated the progression of cognitive impairment and WMHs in the oldest old.

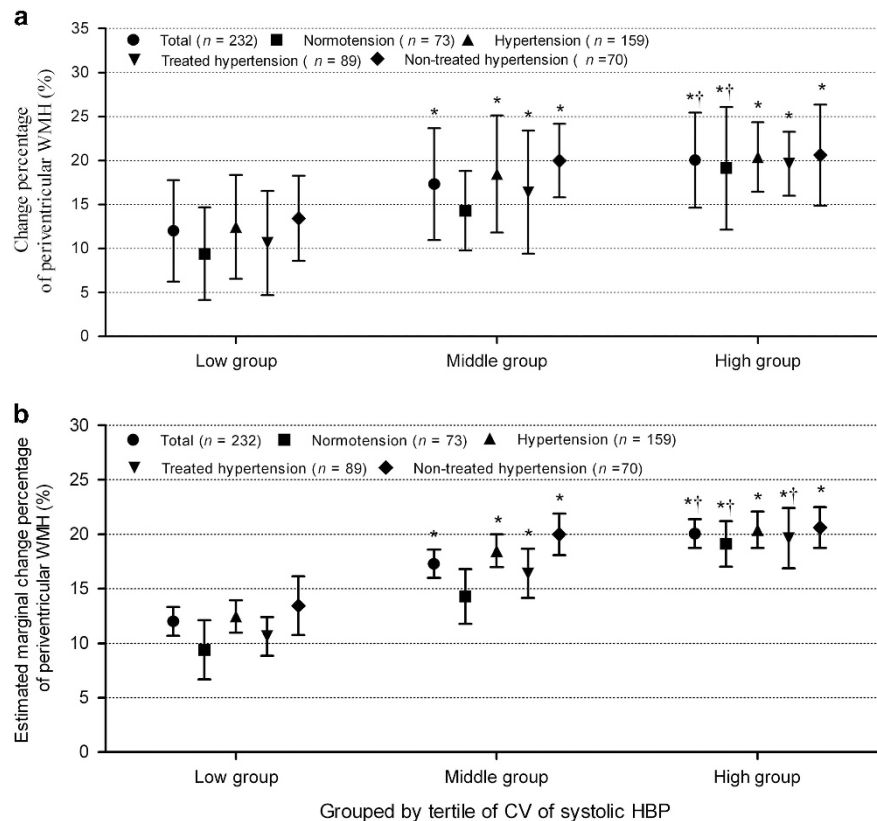


Figure 5 Effect of CV of systolic HBP on change percentage of periventricular white matter hyperintensities during the follow-up period. (a) Shown as mean values with s.d.s. (b) Shown as estimated marginal mean values with 95% confidence intervals resulting from the analysis of covariance model adjusted for age, sex, the baseline body mass index, the baseline official blood pressure, the baseline blood lipid and glucose, education, smoking, alcohol consumption and the baseline periventricular white matter hyperintensities. WMH indicates white matter hyperintensities. * $P < 0.05$, compared with the Low group; † $P < 0.05$, compared with the middle group.

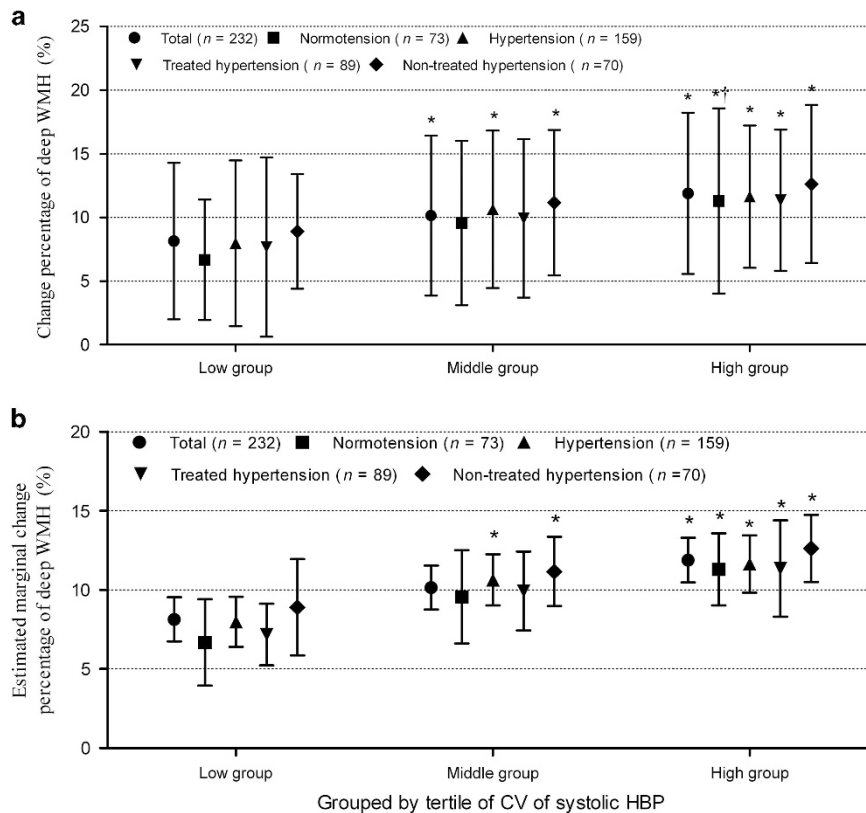


Figure 6 Effect of CV of systolic HBP on change percentage of deep white matter hyperintensities during the follow-up period. (a) Shown as mean values with s.d.s. (b) Shown as estimated marginal mean values with 95% confidence intervals resulting from the analysis of covariance model adjusted for age, sex, the baseline body mass index, the baseline official blood pressure, the baseline blood lipid and glucose, education, smoking, alcohol consumption and the baseline deep white matter hyperintensities. WMH indicates white matter hyperintensities. * $P < 0.05$, compared with the Low group; † $P < 0.05$, compared with the middle group.

Although the relationship between BP level and target organ damage is well established,^{32,33} it remains unclear whether variability in BP is related to cardio- and cerebrovascular diseases.²³ Schutte *et al.*³⁴ reported that variability in BP did not contribute to risk stratification beyond the mean systolic BP in an unbiased general population sample. In contrast, there is increasing evidence of the association of variability in BP with target organ damage and mortality independent of mean BP.^{35–38} The Honolulu-Asia Aging study³⁵ revealed that higher variability in SBP in midlife significantly increased the risk of WMLs and atrophy. The Ohasama study³⁶ demonstrated that day-to-day variability in systolic HBP is markedly associated with cognitive decline after adjusting for mean systolic HBP (odds ratio was 1.51, $P = 0.02$). Consistent with these findings, our exploratory analyses indicated that excessive variability in systolic HBP, assessed by CV of systolic HBP, is an independent contributor to the MMSE score decline and WMH and WMH fraction increases in the oldest old independent of the classification of the participants into normotensive and hypertensive subjects, and hypertensive patients classification into patients with anti- and non-antihypertensive treatment.

Our results indicated that excessive variability in systolic HBP is a strong contributor to the progression of cognitive function decline and WML increase, including WMLs in different regions of the brain. Excessive CV of systolic HBP significantly contributed to increasing total WMH and WMH fractions, and markedly contributed to increases in periventricular and deep WMH in all subjects although they were categorized into normotension, hypertension, antihypertension and non-antihypertension groups. It may be related to

dysfunction of the autonomic nervous system and advance arterial stiffness, which are common among elderly people, particularly the oldest old. Higher variability in systolic HBP, which contributes to frequent hypotension episodes, can result in cerebral hypoperfusion with consequent cerebral small vessel disease³⁹ and hippocampal atrophy⁴⁰ and accelerate cognitive impairment.⁴¹ Moreover, aggressive fluctuations of systolic blood pressure may result in hemodynamic instability in the systemic circulation and induce low or even oscillatory shear stress on the vascular wall.^{42,43} These shear stresses result in vascular endothelial dysfunction and micro-cerebral vessel damage, which subsequently destroy the structure and function of the brain.⁴²

In the present study, we found that there were no significant differences in the decreased percentages of the MMSE score and increased percentages of WMH and WMH fractions between participants with normotension and hypertension during the follow-up period. This may have occurred because the hypertensive patients included patients with antihypertensive and non-antihypertensive therapy. The results of the present study revealed that the decreased percentages of the MMSE score and increased percentages of WMH and WMH fractions in patients with non-antihypertensive therapy were significantly greater compared with patients with antihypertensive therapy.

One of the major strengths of our study is that the BP profiles were assessed using seven consecutive days of self-measured BP monitoring by participants at home. As previously described, HBP more accurately reflects an individual's BP than the official BP, and provides variability

in BP under relatively well-controlled conditions.^{21–26} To the best of our knowledge, this is the first study of the effect of variability in systolic HBP on the progression of cognitive impairment and WMLs in the oldest old. Furthermore, to determine this effect, we classified the oldest old into normotensive subjects and hypertensive patients, and hypertensive patients were categorized into patients with and without antihypertensive treatment. In addition, the function, structure, and region of the WHLs in the brain were evaluated using the MMSE score, periventricular WMH, deep WMH, total WMH and WMH fractions in the present study.

However, limitations in the present study must be considered. First, all data in our study are observational in nature with known limitations. Second, this study included more females than males, which may have introduced bias in the results of analyses, as sex is a confounding factor for cognitive impairment and WMLs.⁴⁴ Third, a small number of oldest old was enrolled in this study. A larger sample is needed in future studies.

CONCLUSIONS

In conclusion, excessive variability in systolic HBP exacerbates the progression of cognitive dysfunction and brain WMLs in the oldest old. Variability in systolic BP, particularly variability in systolic HBP, should be fully considered in the management of BP and daily life in the oldest old.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Design and conduct of the study: Zhendong Liu, Yingxin Zhao, Guosheng Jiang. Data collection and analysis: Zhendong Liu, Yingxin Zhao, Hua Zhang, Qiang Chai, Yi Cui, Yutao Diao, Jianchao Xiu, Xiaolin Sun. Data interpretation and manuscript writing: Zhendong Liu, Yingxin Zhao, Hua Zhang.

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