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ORIGINAL RESEARCH

Long-Term Visit-to-Visit Blood Pressure Variability and Cognitive Decline Among Patients With Hypertension: A Pooled Analysis of 3 National Prospective Cohorts

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BACKGROUND: A limited number of studies investigated the association between blood pressure variability (BPV) and cognitive impairment in patients with hypertension. This study aimed to identify the longitudinal association between BPV and cognitive decline and the role of blood pressure (BP) control in this association.

METHODS AND RESULTS: Participants with hypertension from the HRS (Health and Retirement Study), the ELSA (English Longitudinal Study of Ageing), and the CHARLS (China Health and Retirement Longitudinal Study) were included. Variation independent of the mean (VIM) was adopted to measure BPV. Cognitive function was measured by standard questionnaires, and a standardized *Z* score was calculated. Linear mixed-model and restricted cubic splines were adopted to explore the association between BPV and cognitive decline. The study included 4853, 1616, and 1432 eligible patients with hypertension from the HRS, ELSA, and CHARLS, respectively. After adjusting for covariates, per-SD increment of VIM of BP was significantly associated with global cognitive function decline in *Z* scores in both systolic BP (pooled β, −0.045 [95% CI, −0.065 to −0.029]) and diastolic BP (pooled β, −0.022 [95% CI, −0.040 to −0.004]) among hypertensive patients. Similar inverse associations were observed in patients with hypertension taking antihypertensive drugs and in patients with hypertension with well-controlled BP.

CONCLUSIONS: High BPV was independently associated with a faster cognitive decline among patients with hypertension, even those with antihypertensive medications or well-controlled BP. Further studies are needed to confirm our results and determine whether reducing BPV can prevent or delay cognitive decline.

Key Words: blood pressure variability ■ cognitive decline ■ pooled analysis

Dementia, characterized by cognitive impairment, has become a global public health issue.[1] Statistics from the World Health Organization demonstrate that >55 million people throughout the world have dementia, and enormous economic loss is contributed by dementia.[2] More than 1 billion adults worldwide have hypertension,[3] and it is a pernicious risk for cognitive impairment and dementia.[4] Midlife hypertension causes a 25% increase in Alzheimer dementia risk.[5] It is of critical importance to control and prevent cognitive impairment among patients with hypertension.

A growing body of evidence indicates that oscillations in blood pressure (BP) between consecutive

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CLINICAL PERSPECTIVE

What Is New?

- High blood pressure variability was associated with faster cognitive decline among patients with hypertension, even those with antihypertensive medications or well-controlled blood pressure.

What Are the Clinical Implications?

- Our results suggest that not only controlling blood pressure but also managing blood pressure oscillations should be paid close attention to patients with hypertension.

Nonstandard Abbreviations and Acronyms

ARV	Average Real Ariability
ASPREE	Aspirin in Reducing Events in the Elderly
BPV	Blood Pressure Variability
CHARLS	China Health and Retirement Longitudinal Study
CV	Coefficient of Variation
ELSA	English Longitudinal Study of Ageing
HRS	Health and Retirement Study
VIM	Variation Independent of the Mean

measures hold additional prognostic significance for the risk of cardiovascular diseases and subclinical target organ damage, including brain function.[6] Previous studies have reported associations of high BP variability (BPV) with dementia and global cognitive impairment in the general population.[7–9] However, a limited number of studies investigated the association between BPV and cognitive impairment in patients with hypertension. Whether there are differences in the effects of BPV on cognition dimensions is worth further investigation.

Therefore, this study aimed to identify the longitudinal association between BPV and cognitive decline among hypertensive patients, patients taking antihypertensive drugs, and patients with well-controlled BP across 3 national cohorts. Further, we aimed to examine the potential effect of modification on these associations.

METHODS

All data have been made publicly available at the HRS (Health and Retirement Study; https://hrs.isr.umich.edu/), the ELSA (English Longitudinal Study of Ageing; https://www.elsa-project.ac.uk/), and the CHARLS (China Health and Retirement Longitudinal Study; https://charls.pku.edu.cn/en/).

Study Population

The data were derived from the HRS, ELSA, and CHARLS. The HRS is a nationally longitudinal panel study of the United States, which was conducted in 1992 and followed up every 2 years. It covers a wide range of contents, including health, work and retirement, social connections, and economic status, which is the most comprehensive population-representative study of aging in the United States. The collection and production of HRS data comply with the requirements of the University of Michigan's Institutional Review Board and participants gave informed consent.[10] Both the ELSA and the CHARLS are sister surveys of the HRS. The ELSA was also a panel study of representative cohorts of population aged ≥50 years living in England, which was set up in 1998 and followed up every 2 years to document the information of the aging population. All waves and components had obtained ethical approval and ethical consent.[11] The CHARLS was a nationally representative longitudinal survey of Chinese >45 years, and it was initiated from June 2011 and participants were tracked every 2 to 3 years. It was approved by the Ethical Review Committee at Peking University, and all participants signed informed consent before participation.[12]

In the study, Wave 2006 to Wave 2018 from the HRS, Wave 2002 to Wave 2016 from the ELSA, and Wave 2011 to Wave 2018 from CHARLS were included, respectively. All patients with hypertension with at least 3 visits were used in the analyses. The exclusion criteria of all 3 cohorts were as follows: (1) with missing information on cognitive function tests, BP measurement, and covariates; (2) taking medication for heart problems or being diagnosed with heart-related diseases (heart attack, coronary heart disease, angina, congestive heart failure, heart murmur, abnormal heart rhythm, and other heart problem), or cognition-related diseases (Alzheimer disease, dementia, and memory problems) at baseline; and (3) lost to follow-up. Finally, there were 4853, 1616, and 1432 eligible patients with hypertension from the HRS, ELSA, and CHARLS available for analyses, respectively (Figure S1).

Definition of Hypertension and BPV

Automatic BP monitors (Omron HEM-780 Monitor for the HRS, Omron HEM-907 Monitor for the ELSA, and Omron HEM-7200 Monitor for the CHARLS; Omron Healthcare, Inc., Bannockburn, IL) were used to measure BP in the 3 cohorts. Participants were instructed to be seated with their left arms supported and palm facing up. The cuff was placed on their arms,

ensuring direct skin contact, positioned about half an inch above the elbow, with the air tube in the middle. BP in their left arms was measured 3 times with 45- to 60-second intervals between each. In the HRS and the ELSA, participants' BP was monitored every 4 years, whereas the CHARLS conducted BP assessments biennially (Table S1).

In this study, hypertension was defined as a 3-times average systolic BP of ≥140 mm Hg or diastolic BP ≥90 mm Hg, or taking antihypertensive drugs at baseline.[13] Well-controlled BP was defined as hypertensive participants having a systolic BP <140 mm Hg and a diastolic BP <90 mm Hg at any 1 time during the follow-up.[14]

In the main analysis, variation independent of the mean (VIM) was adopted to indicate the BPV across visits given that alternate measures have previously been shown as highly correlated with the mean BP, thus limiting their ability to differentiate from the effects of mean BP.[15] The VIM was calculated as 100× SD/mean$^{\beta}$, where the β was the regression coefficient based on the natural logarithm of the SD over the natural logarithm of the mean.[16] In the sensitivity analysis, the coefficient of variation (CV) and average real variability (ARV) were used to assess the BPV. The CV was computed by dividing the SD by the average BP. The ARV was calculated as the average of the absolute differences between BP measurements across visits.

Measurement of Cognitive Function

Cognitive function in all 3 cohorts was measured every 2 years via standard questionnaires, which included memory function, orientation function, and executive function (Tables S1 and S2). The memory function was assessed by tests of immediate and delayed word recall. The orientation function was measured by asking participants about the year, month, day, day of week (and season) of the tests. The executive function in the CHARLS was assessed by serial 7s subtraction (100–7), and the HRS also included a backward count from 20. The executive function in the ELSA was conducted via an animal-naming fluency test. For all tests, a higher score represented a better performance, and the global cognitive function in the study was defined as the sum of scores of 3 dimensions.[10–12] The validity and consistency of the above tests have been verified by previous studies.[17–19] The details of cognitive function tests were shown in Data S1 and Tables S1 and S2.

Covariates

In all 3 studies, participants' demographic information and lifestyles were collected via standard questionnaires face to face. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

In the HRS, high-level education referred to those who have a diploma from high school and above (≥12 years). Current smokers were defined as those who "smoke cigarettes now," and current drinkers were participants who drank any alcohol in the past 3 months before the baseline survey. In the ELSA, high-level education was defined as an educational qualification of NVQ3/GCE A level and above. Current smokers represented participants who "smoke cigarettes at all nowadays." Current drinkers referred to respondents who consumed alcohol at least 1 day of the last week before the survey. In the CHARLS, a diploma of junior high school and above was categorized as high-level education attainment. Current smokers were classified as smoking at least 1 cigarette per day, and current drinkers were the participants who consumed any alcoholic beverages more than once a month in the past years.

Statistical Analysis

Continuous variables were expressed as means±SD ($\bar{x}\pm s$), and categorical variables were reported as percentages (n [%]). A linear mixed model adjusting for age, sex, baseline BP, body mass index, marital status, education attainment, smoking, drinking, race, and residential areas (rural/urban, only available in the CHARLS) was adopted to explore the longitudinal association between per SD increment of BPV and cognitive function decline (R lme4 package).[20] All the covariates were considered fixed effects, and study waves were treated as random effects. To ensure the comparability of cognitive function measurement in 3 cohorts, a standardized Z score for all dimensions and global cognitive function was calculated by subtracting the mean score at baseline and dividing the value by the SD of the scores at baseline.[21] Stratified analyses were performed by sex (male versus female) and age at baseline (<65 versus ≥65). Potential effect modifications were assessed by adding interaction terms between the above factors and per SD increment of BPV to the linear mixed models. In addition, the restricted cubic splines with 4 knots (had the lowest Akaike information criterion value) were applied to explore the nonlinear associations between per SD increment and the cognitive function performance at the last visit (R rcs package; R Foundation for Statistical Computing, Vienna, Austria). The pooled effects in this study were calculated using random-effects meta-analysis. The heterogeneity of β values among the 3 cohorts was evaluated by Cochran's Q test and I^2 statistic. In a sensitivity analysis, the associations of per-SD increment of ARV and CV with cognitive function decline were assessed, respectively. In another sensitivity analysis, we conducted the same analyses including heart condition as a covariate.

All analyses were performed with Stata 16.0 (StataCorp., College Station, TX) and R 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided $P<0.05$ was considered statistically significant.

RESULTS

General Characteristics

There were 4853, 1616, and 1432 eligible patients with hypertension with at least 3 measurements of BP from the HRS, ELSA, and CHARLS available for analyses, respectively. The baseline characteristics of the 3 cohorts are shown in the Table and Tables S3 through S5. The mean age was 65.32±9.08 years for participants in the HRS, 64.59±8.34 years for participants in the ELSA, and 59.57±8.34 years for participants in the CHARLS. Baseline characteristics between included and excluded participants of the 3 cohorts are demonstrated in Tables S6 through S8.

Association Between VIM of BPV and Cognitive Function Decline

The trend of cognitive function test score changes among patients with hypertension in tertiles of VIM of SBP across visits is shown in Figure 1. Patients with hypertension in the tertile 3 group had lower scores in 3 studies.

Overall, after adjusting for age, sex, body mass index, marital status, education attainment, baseline BP, smoking, drinking, race, and residential areas, per-SD increment of VIM of BP was significantly associated with global cognitive decline in *Z* scores in both systolic BP (pooled β, −0.045 [95% CI, −0.065 to −0.029]) and diastolic BP (pooled β, −0.022 [95% CI, −0.040 to −0.004]) among patients with hypertension. Further adjusting for antihypertensive drug treatment, the results demonstrated parallel trends (Figure S2). Additionally, there was no significant nonlinear association found between per-SD increment of VIM of BP and the *Z* score of cognitive function tests (Figure 2).

Similarly, inverse associations were also observed in patients with hypertension taking antihypertensive drugs (pooled β, −0.060 [95% CI, −0.082 to −0.038] for systolic BP) and (pooled β, −0.024 [95% CI, −0.047 to −0.002] for diastolic BP) in patients with hypertension with well-controlled BP (pooled β, −0.063 [95% CI, −0.089 to −0.037] for systolic BP; and pooled β, −0.029 [95% CI, −0.055 to −0.002] for diastolic BP).

Further, the association of BPV with cognitive decline was stronger in the systolic BP than diastolic BP, where the result of pooled analyses in global cognitive

Table 1. Main Baseline Characteristics of Participants

Hypertensive patients			
Characteristics	**HRS (n=4853)**	**ELSA (n=1616)**	**CHARLS (n=1432)**
Age, y	65.32±9.08	64.59±8.34	59.57±8.34
Female sex, %	2921 (60.19)	846 (52.35)	689 (48.11)
High-level education, %	3881 (79.97)	573 (35.46)	480 (33.52)
SBP at baseline, mmHg	137.10±19.41	146.90±15.38	148.56±18.37
DBP at baseline, mmHg	84.01±11.71	81.25±10.92	85.01±11.73
Patients with hypertension taking antihypertensive drugs			
Characteristics	**HRS (n=3662)**	**ELSA (n=564)**	**CHARLS (n=630)**
Age, y	65.81±8.87	64.42±8.22	59.72±7.95
Female sex, %	2295 (62.67)	314 (55.67)	327 (51.90)
High-level education, %	2930 (80.01)	182 (32.27)	220 (34.92)
SBP at baseline, mmHg	133.17±19.28	137.55±16.90	142.73±21.08
DBP at baseline, mmHg	81.31±11.26	76.41±10.79	81.84±12.34
Patients with hypertension with well-controlled blood pressure			
Characteristics	**HRS (n=3044)**	**ELSA (n=457)**	**CHARLS (n=395)**
Age, y	65.52±8.69	64.51±8.14	59.66±8.06
Female sex, %	1913 (62.84)	247 (54.05)	222 (56.20)
High-level education, %	2465 (80.98)	154 (33.70)	131 (33.16)
SBP at baseline, mmHg	131.02±18.07	136.22±16.89	137.36±19.68
DBP at baseline, mmHg	80.63±10.91	76.02±10.82	79.93±11.69

CHARLS indicates China Health and Retirement Longitudinal Study; DBP, diastolic blood pressure; ELSA, English Longitudinal Study of Aging; HRS, Health and Retirement Study; and SBP, systolic blood pressure.

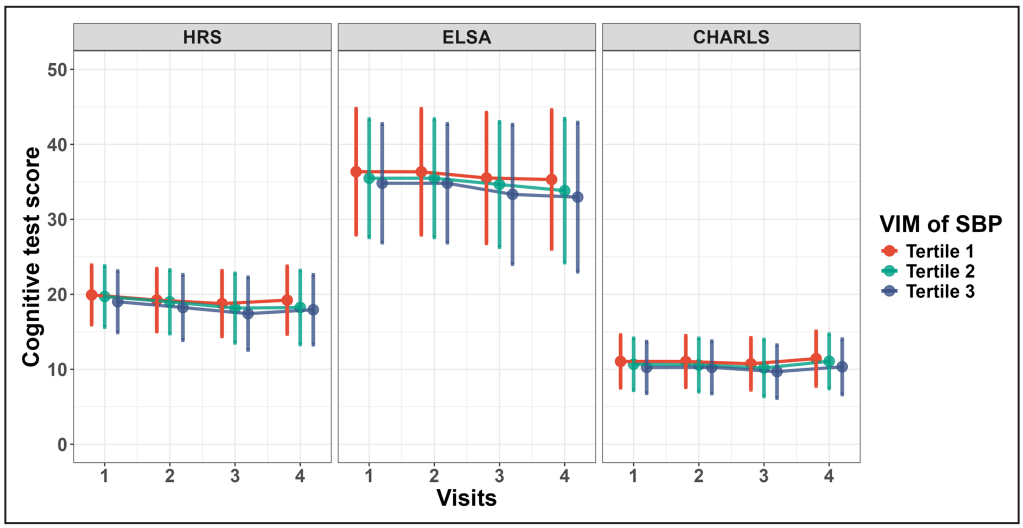

Figure 1. Cognitive test score change of patients with hypertension in tertiles of variation independent of the mean (VIM) of systolic blood pressure (SBP) across visits.
The solid dots represent the average scores, and the error bars represent the 95% CIs. CHARLS indicates China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; and HRS, Health and Retirement Study.

function and all dimensions showed statistically significant associations, and 3 cohorts demonstrated parallel tendency. The inverse associations of BPV for diastolic BP with the decline of orientation function and executive function were not statistically significant (Figure 3).

Subgroup and Sensitivity Analyses

The result of stratified analyses on global cognitive function is shown in Figure 4. We did not observe a statistically significant interaction for sex and age. The results of the 3 dimensions of cognitive function were similar (Figures S3 through S5). The association between per-ARV increment, per-CV increment of BP, and cognitive function changes all remained consistent (Figures S6 and S7). Also, a similar result was observed when including heart condition as a covariate (Figure S8). Nonlinear associations among patients with hypertension taking antihypertensive drugs and patients with hypertension with well-controlled BP were not observed (Figures S9 and S10).

DISCUSSION

In this study, we examined the association between long-term BPV and cognitive function change among patients with hypertension based on 3 national cohorts. We further reported that per-SD increment of BPV, both systolic and diastolic BP, were associated with faster cognitive function decline among patients with hypertension, regardless of whether they took antihypertensive drugs or their BP was well controlled.

Our result showed a positive association between BPV and cognitive decline, which was consistent with previous short-term (normally within a 24-hour period) and long-term (over months, seasons, and years) studies.[6] Another pooled analysis of the HRS and the ELSA reported a significant association between per-10% increment of long-term BPV and global cognitive function decline in the general population, and a nonlinear association was observed.[13] Our result further extended that patients with hypertension taking antihypertensive drugs or even with well-controlled BP still face a faster cognitive decline when they have high BPV. In line with the ASPREE (Aspirin in Reducing Events in the Elderly) trial, high BPV in older adults without major cognitive impairment is associated with increased risks of dementia and cognitive decline, independent of average BP and use of antihypertensive drugs.[22] Some studies reported that the association between BPV and cognitive decline was stronger in men than in women[23] and in populations aged >65 years than in populations aged ≤65 years in the general population,[24] but current evidence is inconsistent.[25] In our study, we did not find any significant interaction effects for age and sex, which might be related to the small sample size of each subgroup after stratification.

The underlying mechanisms between BPV and cognitive decline remain incompletely clear. Some previous evidence indicated that high BPV (whether short term or long term) may elevate shear stress on the vessel wall, potentially resulting in endothelial damage, impaired smooth muscle function, and inflammation within the vasculature.[26,27] The early inflammatory response is believed to elevate the long-term susceptibility to dementia.[28]

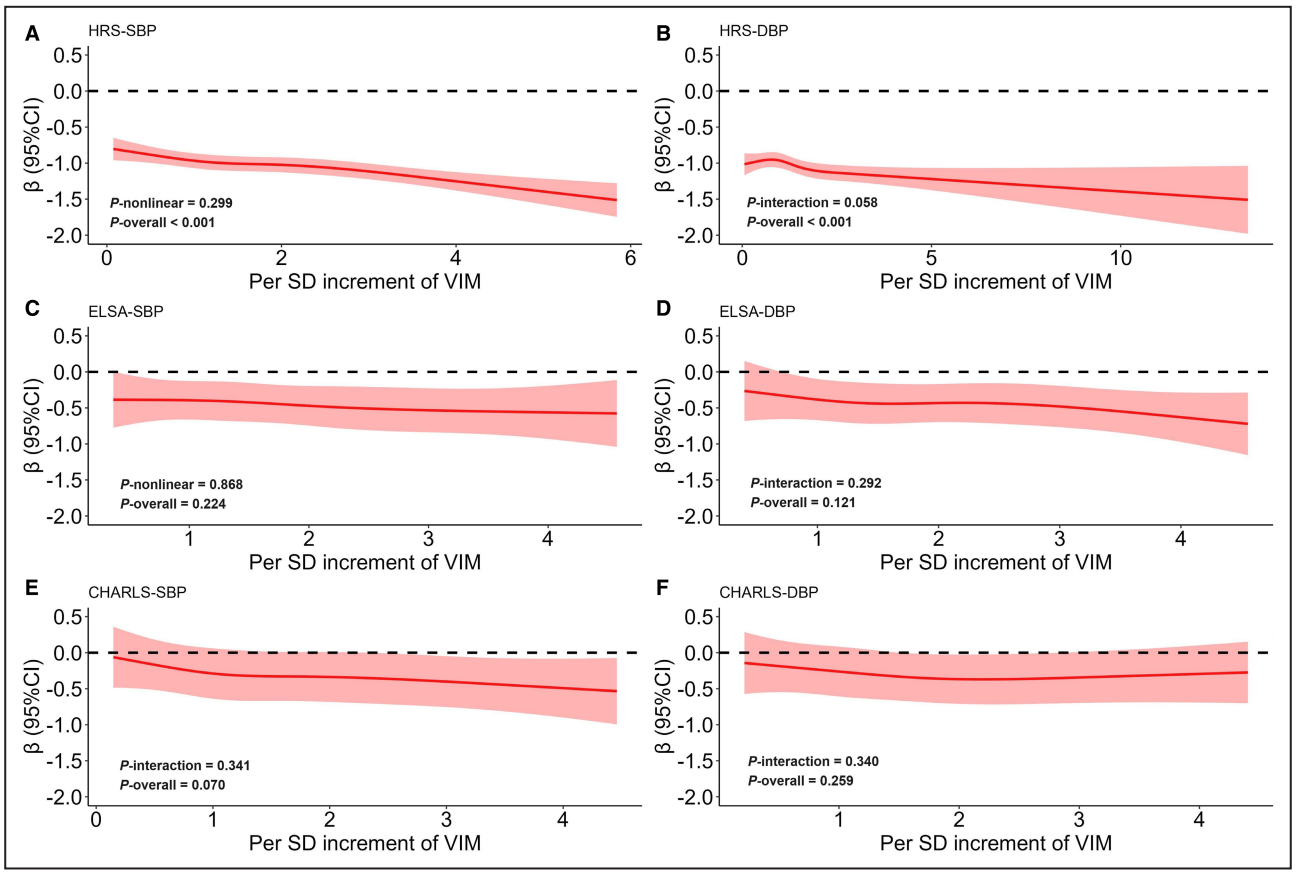

Figure 2. Nonlinear association between per- SD increment of variation independent of the mean (VIM) of blood pressure and the global cognitive function decline among hypertensive patients.
The solid lines represent the point estimates, and the shaded parts represent the 95% CIs in each cohort. CHARLS indicates China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; and HRS indicates Health and Retirement Study.

Endothelial dysfunction triggered by injury will prompt heightened secretion of proinflammatory cytokines, contributing to neurovascular unit impairment.[29] Moreover, it is suggested that higher systolic BPV during adulthood was correlated with diminished normal tissue volumes in critical brain regions such as the hippocampus, gray matter, and overall brain volume, which may increase the risk of cognitive decline or dementia.[30] In addition, greater BPV in midlife was also related to the increase of later-life brain atrophy and the decline of white matter integrity.[31] Furthermore, it is reported that older age and hypertension are associated with higher BPV,[32,33] which leads to vulnerability to minor stressors, and then endothelial dysfunction and increase in systemic vascular resistance.[34] Therefore, a higher long-term BPV in patients with hypertension could be a reflection of this lower resilience. Although causes of high BPV are still under debate and are thought to differ between long- and short-term BPV, arterial compliance, sympathetic drive, and behavioral factors are likely to be involved.[35] It is also possible that the causal association between BPV and cognitive dysfunction are bidirectional, or nonexistent but stem from a common cause, such as small-vessel disease.[36] The underlying mechanisms may involve a series of biological changes and need to be further studied.

Our study has several strengths:

1. We further reported that high BPV was associated with faster cognitive function decline in patients with hypertension, regardless of whether they took antihypertensive drugs or their BP was well controlled.
2. Participants of this study derived from 3 independent national cohorts, which extends the extrapolation of results.
3. Multiple measurement indicators were adopted to reflect BPV, including VIM, ARV, and CV, enhancing the robustness of our results.

There were also some limitations to our study. First, the residual confounding and reverse causality cannot be fully excluded due to the nature of this observational study. Second, although the ELSA and the CHARLS are both the sister cohorts of the HRS, there are significant heterogeneities among these cohorts due to

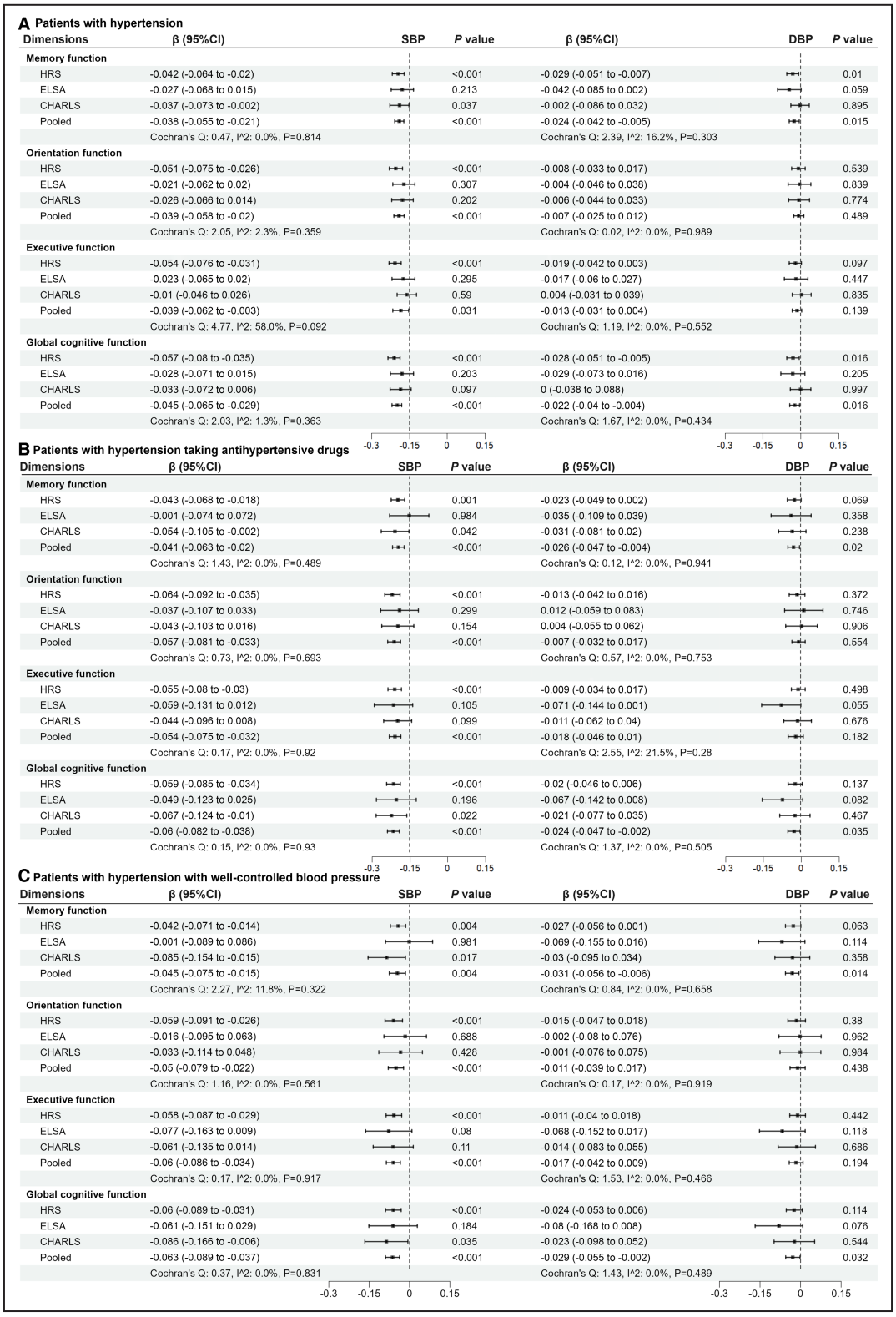

Figure 3. Association between variation independent of the mean (VIM) of blood pressure and cognitive function decline among 3 cohorts.

The small squares represent the β values, and the error bars represent the 95% CIs in each cohort. Adjusted for age, sex, body mass index, smoking, drinking, education attainment, marital status, and BP at baseline. Models for the HRS and the ELSA additionally adjusted for ethnicity, and models for the CHARLS additionally adjusted for residential areas (urban/rural). CHARLS indicates China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; and HRS, Health and Retirement Study.

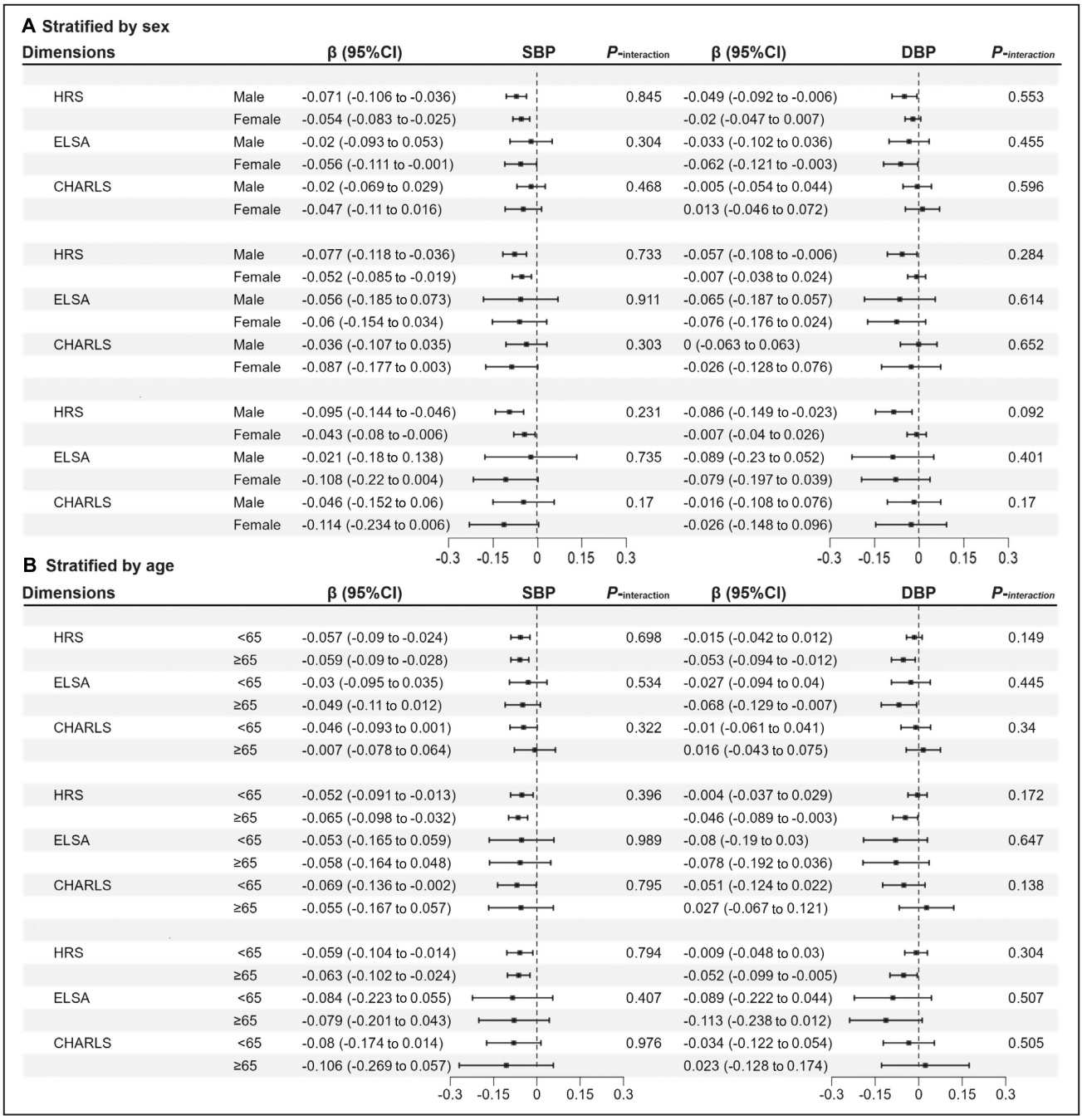

Figure 4. The result of subgroup analyses by sex and age on global cognitive function decline among 3 cohorts.
The small squares represent the β values, and the error bars represent the 95% CIs in each cohort. CHARLS indicates China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; and HRS, Health and Retirement Study.

different countries and cultures. Third, it is reported that the types and adherence to antihypertensive drugs had different influences on the BPV,[37,38] but we cannot obtain this detailed information. Fourth, 3 to 4 measurements of BP may not accurately reflect the true long-term variability. Finally, although our study demonstrated that elevated BPV is linked to cognitive decline among patients with hypertension, whether reducing BPV can prevent or delay cognitive decline remains unclear.

CONCLUSIONS

In summary, we further reported that high BPV was associated with faster cognitive decline among patients with hypertension, even those taking antihypertensive

medications or with well-controlled BP. The results suggest that not only controlling BP but also managing BP oscillations should be given close attention in patients with hypertension. Further randomized controlled trials or Mendelian randomization studies are needed to confirm our results and determine whether reducing BPV can prevent or delay cognitive decline.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Data S1
Tables S1–S8
Figures S1–S10

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