ORIGINAL RESEARCH

Long-Term Blood Pressure Level and Variability From Midlife to Later Life and Subsequent Cognitive Change: The ARIC Neurocognitive Study

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***Background*—**To understand how blood pressure (BP) from midlife and beyond is related to cognition in older age, a lifespan approach is needed. We assessed the associations of BP levels and variability from midlife on with subsequent cognitive change.

***Methods and Results*—**The ARIC (Atherosclerosis Risk in Communities) Study participants underwent 4 clinic BP measurements (visit 1, 2, 3, and 4 BPs) between 1987 and 1998, and their mean levels and average real variability (ARV) were assessed as exposures. A global cognitive *z* score, estimated from the Delayed Word Recall Test, Digit Symbol Substitution Test, and Word Fluency Test scores, was calculated at 1996 to 1998 (visit 4) and 2011 to 2013 (visit 5). Among 11 408 participants (mean age, 54 years; 56% women; 21% black race), mean systolic BP (SBP)/diastolic BP (DBP) level was 123/72 mm Hg, and ARV_{SBP}/ARV_{DBP} was 11/7 mm Hg. With linear mixed models, 1-SD increases of ARV_{SBP} (standardized regression coefficient [95% confidence interval], −0.03 [−0.04 to −0.01] points) and ARV_{DBP} (standardized regression coefficient [95% confidence interval], −0.02 [−0.03 to −0.002] points; both $P<0.05$), but not mean SBP or DBP levels, were associated with lower global cognitive *z* scores at visit 4. In contrast, mean SBP (standardized regression coefficient [95% confidence interval], −0.04 [−0.06 to −0.02] points) or DBP (standardized regression coefficient [95% confidence interval], 0.04 [0.02–0.06] points; both $P<0.001$) level, but not ARV_{SBP} or ARV_{DBP}, was associated with change in global cognitive *z* scores from visits 4 to 5.

***Conclusions*—**Greater visit-to-visit SBP or DBP variability from midlife on is modestly associated with lower cognitive function, whereas higher mean SBP and lower DBP levels from midlife to later life are modestly associated with cognitive decline in later life.
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Key Words: blood pressure • blood pressure variability • cognition

Evidence supporting a link between midlife blood pressure (BP) levels and late-life cognitive outcomes continues to accumulate.[1–12] In addition to BP levels, BP variability may be associated with cognitive function.[12–18] BP variability consists of short-term BP variability (eg, within 24 hours) and long-term BP variability (eg, visit-to-visit BP variability).[19,20] However, it is unclear whether associations differ between long-term BP levels versus BP variability during midlife and cognitive decline in later life.

The association between greater long-term BP variability and lower cognitive function has been recently highlighted in European and Asian studies,[13–18] although reports from studies of US populations are limited. Cognitive function was assessed at a single time point in these European and Asian studies[13–15] and, thus, it remains to be determined whether long-term BP variability is associated with cognitive function only concurrently or whether it is also related to individual cognitive decline. Given that greater long-term BP variability with long-term periods of higher and lower BP levels has been related to increased cerebrovascular damage or cerebral hypoperfusion,[12,19,20] we hypothesized that greater long-term BP variability in midlife would be associated with a steeper decline in cognitive function in later life.

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Accompanying Tables S1 through S20 and Figures S1 through S3 are available at http://jaha.ahajournals.org/content/7/15/e009578/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Greater visit-to-visit systolic blood pressure (BP) or diastolic BP variability from midlife on is associated with lower cognitive function, whereas higher mean systolic BP and lower diastolic BP levels from midlife to later life are associated with more rapid cognitive decline in later life.

What Are the Clinical Implications?

- Assessment of both BP variability and levels in midlife may be useful in identifying individuals at high risk of cognitive dysfunction in later life.

To understand the association of BP in midlife with cognition in older age, a lifespan approach is crucial. However, conducting lifespan studies is challenging because of the many years of follow-up required. We are uniquely positioned to fill these knowledge gaps using data from the ARIC (Atherosclerosis Risk in Communities) Study. The ARIC Study enrolled middle-aged black and white individuals and measured clinic BP and cognitive function over a 25-year period. Using data from the ARIC Study, we sought to assess whether long-term BP levels and variability in midlife are associated with cognitive change in later life.

Methods

Requests for the data, analytic methods, and study materials used in this study for purposes of reproducing the results or replicating the procedure may be submitted to the ARIC Study publications committee.

Study Population

Details of the study rationale, design, and procedures have been published previously.[21] Briefly, 15 792 black and white adults, aged 45 to 64 years, were enrolled into the ARIC Study between 1986 and 1990 via probability sampling from 4 US communities: Washington County, Maryland; Forsyth County, North Carolina; Minneapolis, MN, suburbs; and Jackson, MS. Participants underwent 5 examinations during 25 years of follow-up (ie, visit 1, 2, 3, 4, and 5 examinations; Figure 1), with an annual contact by telephone. In the current analysis, we used BPs from visit 1 (1987–1989) through visit 4 (1996–1998) and cognitive function test scores at visit 4 and visit 5 (2011–2013). The institutional review board at each study center approved the methods, and informed participant consent was obtained.

BP and Other Measurements

Trained study personnel and research technicians took all physical measurements and administered all questionnaires following a standardized protocol, including quality control measures.[21] The technicians obtained 3 seated BP readings after participants had been sitting in a quiet room for 5 minutes, using random-zero sphygmomanometers. The average of the second and third BP measurements was used for analysis. Pulse pressure (PP) was calculated as systolic BP (SBP) minus diastolic BP (DBP).

For BP variability measurements, we calculated the SD (SD_{SBP} and SD_{DBP}) and coefficient of variation (CV; CV_{SBP} and CV_{DBP}) on the basis of visit 1, 2, 3, and 4 BPs (Figure 1). These measures have been used in previous studies of BP variability.[13–18] Average real variability (ARV) is the average absolute difference between successive BP measurements and, in contrast with SD and CV, it takes into account the order of the clinic visits at which BP was measured.[19,20] Herein, we report only SD and ARV as BP variability measures, because CV is strongly correlated with SD (Pearson's r >0.95; Table S1). However, SD and ARV are partially dependent on the overall BP level and change in mean BP levels over time. Distinguishing BP variability from systemic changes in BP level over time could, thus, be difficult.[22] The issue may not be resolved even if we use mean BP level over visits as an adjustment factor. Therefore, in a sensitivity analysis, we also estimated BP variability independent of the mean (VIM).[20,22] We also calculated mean SBP and DBP levels from visit 1 to visit 4.

Educational attainment, lifestyle (ie, smoking and drinking status), medical history, and laboratory values (ie, glucose and lipid parameters and apolipoprotein E ε4 allele) were collected using standardized protocols and quality control across study centers and examinations. Diabetes mellitus was defined as self-reported history of a physician's diagnosis, diabetes mellitus medication use, fasting blood glucose level ≥126 mg/dL, or nonfasting glucose level ≥200 mg/dL.

Cognitive Function Assessment

A battery of standardized tests, including the Delayed Word Recall Test,[23] the Digit Symbol Substitution Test,[24] and the Word Fluency Test,[25] were conducted at visits 2, 4, and 5 in a quiet room by trained examiners. The recordings were reviewed for quality control. The Delayed Word Recall Test evaluates verbal learning and short-term memory. Participants learned 10 words, used them in sentences, and, after 5 minutes, were asked to recall them. The score was the number of words recalled (maximum of 10).[24] The Digit Symbol Substitution Test evaluates executive function and processing speed. Participants used a key to write symbols corresponding to numbers in 90 seconds. The score, ranging from 0 to 93, was the number of correctly written symbols.[25]

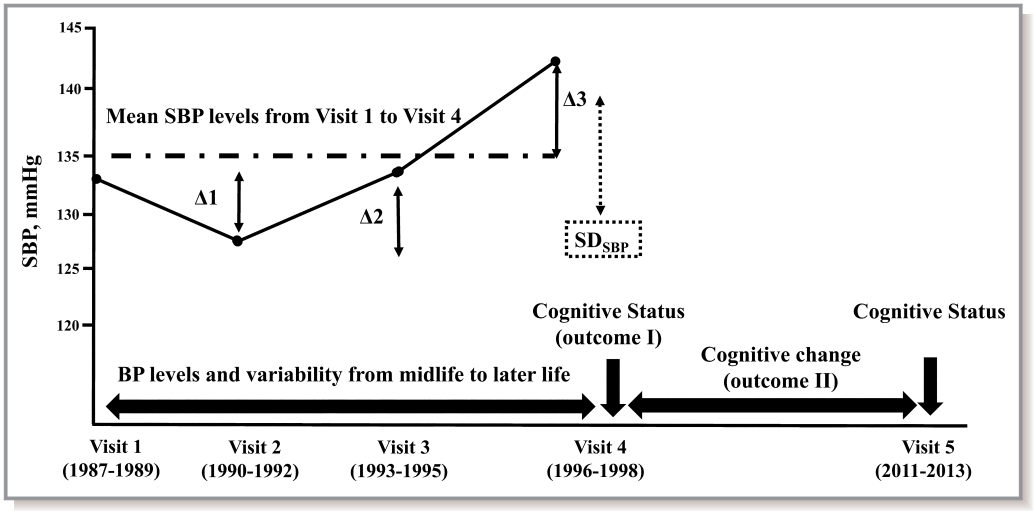

Figure 1. Schematic overview of the study design and the formula of blood pressure (BP) measures. The figure shows one example of individual follow-up systolic BP (SBP) data from visit 1 to visit 4. The absolute differences of SBP between successive SBP measurements are shown as $\Delta 1-\Delta 3$. For example, $\Delta 1$ represents the difference in SBP between the visit 1 and visit 2 values. Average real variability is calculated as follows: $(\Delta 1+\Delta 2+\Delta 3)/3$. Mean SBP levels and SD were calculated from all 4 SBP values from visit 1 to visit 4 for each individual, and coefficient of variation was calculated as SD$\times$100/mean BP.

The Word Fluency Test evaluates executive function and expressive language. Participants generate as many words as possible within 60 seconds, starting with letters F, A, and S, with 1 trial per letter. The total score was the sum of all correct words generated.[26]

A *z* score was calculated in each test to standardize participants' cognitive scores to the baseline scores (ie, visit 2 scores). Specifically, first, we calculated the mean and SD of Digit Symbol Substitution Test, Delayed Word Recall Test, and Word Fluency Test scores for the entire study population at visit 2. Then, for each test, the baseline population mean was subtracted from each participant's raw score at visit 4 and visit 5, and this difference was divided by the baseline population SD. A global *z* score was created for each participant at visits 4 and 5 by averaging individual *z* scores across the 3 tests among participants with 3 nonmissing scores at each visit. This global *z* score served as a standardized multidomain measure of cognitive performance used to represent global cognitive function.

Statistical Analysis

Descriptive statistics are reported as means and SD and as proportions, where appropriate. The associations of BP variability measurements with clinical characteristics were calculated by Pearson's correlation method or the unpaired *t* test. Linear mixed models were used to evaluate associations between BP levels or variability from visit 1 to visit 4 and cognitive change from visit 4 to visit 5. Linear mixed models use a missing at random assumption and all of the available data from an individual over the full course of follow-up. Measures of BP levels and BP variability were analyzed in 1-SD increments to allow for direct comparison among them. All models included the following: sociodemographic characteristics (age, sex, race, education, apolipoprotein E ε4 alleles, and study site); clinical and behavioral characteristics at visit 4 (body mass index, current smoking, current drinking, total cholesterol, high-density lipoprotein, diabetes mellitus, use of antihypertensive drugs, and prevalent stroke); mean SBP or DBP levels from visit 1 to visit 4; ARV or SD from visit 1 to visit 4; the interaction of the time interval from visit 4 to visit 5 (ie, 15 years) and mean SBP or DBP levels from visit 1 to visit 4; and the interaction of the time interval from visit 4 to visit 5 and ARV or SD from visit 1 to visit 4. On the basis of the individual term (ie, ARV or SD from visit 1 to visit 4), we assessed the associations between each BP variability measurement and cognitive function at visit 4 (outcome I in Figure 1). On the basis of the interaction between ARV and time interval (from visit 4 to visit 5; ie, 15 years) or between SD and time interval, we calculated the additional 15-year decline in cognitive function from visit 4 to visit 5 associated with a 1-SD increase of each BP variability measurement (outcome II in Figure 1).

We conducted sensitivity analyses by: (1) using PP instead of SBP and DBP as the exposure; (2) using BP variability independent of the mean instead of ARV and SD as the exposure of BP variability; (3) assessing heterogeneity of effect between BP variability measurements and cognitive change by sex, race, antihypertensive medication use, or apolipoprotein E ε4 allele, with inclusion of additive

interaction terms; (4) conducting stratified analyses by sex, race, antihypertensive medication use at visit 4, or apolipoprotein E ε4 allele (0 versus ≥1); (5) assessing the BP variability-cognition association by excluding participants who had a history of stroke at visit 4; and (6) and creating inverse-probability-of-attrition weighting generalized estimating equation models, which weighted study participants by the inverse of the probability that they will die or drop out to compensate for underrepresentation of people with characteristics associated with death or dropout (eg, attrition attributable to death and hospitalization among those with higher SBP variability).[27] All statistical analyses were performed using Stata, version 14.0 (StataCorp, College Station, TX). Statistical significance was defined as $P<0.05$ on 2-sided tests.

Results

Among 15 792 participants, we excluded 49 not identified as black or white, 12 with missing BP measurements between visit 1 and visit 4, 56 blacks in Minnesota or Washington, and 4267 with missing cognitive function test results at visit 4 or visit 5, leaving a sample of 11 408 participants for analysis (Table 1). The included participants were slightly younger (54 versus 56 years); showed a lower proportion of male sex (44% versus 47%), black race (21% versus 42%), and antihypertensive medication use (27% versus 40%); and had higher educational attainment and cognitive function compared with those not included in this study (n=4384) (Table S2).

Mean SBP/DBP levels, ARV_{SBP}/ARV_{DBP}, and SD_{SBP}/SD_{DBP} from visit 1 to visit 4 were 123/72, 11/7, and 10/6 mm Hg, respectively (Table S3). Tables S4 and S5 show the associations between BP variability measurements and clinical characteristics at baseline. Higher age, black race, higher body mass index, lower educational attainment, current smoking, and diabetes mellitus were associated with higher SBP and DBP variability. The associations between SD_{SBP} and mean SBP levels and those between ARV_{SBP} and mean SBP levels were significant (Pearson's r=0.43–0.46). In contrast, the associations were modest between SD_{DBP} and mean DBP levels and between ARV_{DBP} and mean DBP levels (Pearson's r=0.16–0.18).

Overall, the global cognitive z score and each task z score declined from visit 4 to visit 5 (all $P<0.001$, Table S6). With adjustments for covariates, higher ARV_{SBP} and SD_{SBP} were associated with a lower global cognitive z score at visit 4 (Table 2), whereas we observed no associations between long-term BP variability measures and decline in global cognitive z score from visit 4 to visit 5 (Table 3). Conversely, a 1-SD higher mean SBP level from visit 1 to visit 4 was associated with a 0.04 decline in global cognitive z score from visit 4 to visit 5 (Table 3). Cognitive task-specific analyses showed similar results (Tables S7 and S8). Higher ARV_{PP} and SD_{PP} were associated with a lower global cognitive z score at visit 4, whereas we observed no associations between long-term BP variability measures and decline in global cognitive z score from visit 4 to visit 5 (Tables S9 and S10). Results were similar when we used VIM instead of ARV and SD as the exposure (Tables S11 and S12). Conversely, a 1-SD higher mean PP level from visit 1 to visit 4 was associated with a 0.09 decline in global cognitive z score from visit 4 to visit 5 (Table S10).

Higher ARV_{DBP} and SD_{DBP} were associated with lower global z scores at visit 4, independent of mean DBP levels from visit 1 to visit 4 (Table 2); results were similar when mean SBP levels instead of mean DBP levels were included in these models. Higher ARV_{DBP} and SD_{DBP} levels were associated with a greater decline in a global z score from visit 4 to visit 5, independent of mean DBP levels from visit 1 to visit 4 (Table 3). However, these associations were no longer significant after an adjustment for mean SBP instead of mean DBP levels (standardized regression coefficient, −0.01 to

Table 1. Clinical Characteristics of Study Cohort at Visit 1 (n=11 408)

Characteristics	Value
Descriptive variable	
Age, y	54.3±5.7
Men, n (%)	5006 (44)
Blacks, n (%)	2403 (21)
Educational level, n (%)	
<High school	2050 (18)
High school	4856 (43)
College	4487 (39)
Body mass index, kg/m^2	27.5±5.1
Current smoker, n (%)	2448 (21)
Current drinker, n (%)	6715 (59)
Antihypertensive medication, n (%)	3117 (27)
SBP, mm Hg	119.4±17.2
DBP, mm Hg	73.1±10.6
PP, mm Hg	46.3±12.6
Total cholesterol, mg/dL	214.5±41.1
High-density lipoprotein, mg/dL	52.1±17.0
Diabetes mellitus, n (%)	788 (7)
APOE ε4 alleles, n (%)	
0	7872 (69)
1	3194 (28)
2	342 (3)

Data are expressed as the mean±SD unless otherwise indicated. APOE indicates apolipoprotein E; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

Table 2. Associations Between Long-Term BP Levels or Variability From Visit 1 to Visit 4 and Cognitive Function at Visit 4 (n=11 408)

Variables	Global *z* Score	
	β (95% CIs)	*P* Value
Model 1		
Mean SBP	−0.001 (−0.02 to 0.02)	0.95
ARV_{SBP}	−0.03 (−0.04 to −0.01)	<0.01
Model 2		
Mean SBP	0.001 (−0.02 to 0.02)	0.90
SD_{SBP}	−0.03 (−0.05 to −0.01)	<0.001
Model 3		
Mean DBP	−0.01 (−0.03 to 0.005)	0.15
ARV_{DBP}	−0.02 (−0.03 to −0.002)	0.02
Model 4		
Mean DBP	−0.01 (−0.03 to 0.01)	0.17
SD_{DBP}	−0.04 (−0.05 to −0.02)	<0.001

ARV, SD, and mean BP were calculated on the basis of visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. Adjusted βs (95% CIs) associated with 1-SD increases of each BP parameter are shown. The 1-SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included the following: demographic variables (age at baseline, sex, race, education, apolipoprotein E ε4 alleles, and study center); clinical characteristics at visit 4 (body mass index, smoking, alcohol, total cholesterol, high-density lipoprotein, diabetes mellitus, use of antihypertensive drugs, and prevalent stroke); interval (from visit 4 to visit 5; ie, 15 years); mean SBP (results were shown in model 1) or mean DBP (results were shown in model 2) level; ARV_{SBP} (result was shown in model 1), SD_{SBP} (result was shown in model 2), ARV_{DBP} (result was shown in model 3), or SD_{DBP} (result was shown in model 4); interval×mean SBP (in models 1 and 2) or interval×mean DBP (in models 3 and 4) levels; and interval×ARV_{SBP} (in model 1), interval×SD_{SBP} (in model 2), interval×ARV_{DBP} (in model 3), or interval×SD_{DBP} (in model 4). Statistical significance was defined as $P<0.05$. ARV indicates average real variability; BP, blood pressure; CI, confidence interval; DBP, diastolic BP; SBP, systolic BP.

Table 3. Associations Between Long-Term BP Levels or Variability From Visit 1 to Visit 4 and Cognitive Change From Visit 4 to Visit 5 (n=11 408)

Variables	Global *z* Score	
	β (95% CIs)	*P* Value
Model 1		
Mean SBP*	−0.04 (−0.06 to −0.02)	<0.001
ARV_{SBP}*	0.003 (−0.02 to 0.03)	0.79
Model 2		
Mean SBP*	−0.04 (−0.07 to −0.02)	<0.001
SD_{SBP}*	0.01 (−0.01 to 0.03)	0.42
Model 3		
Mean DBP*	0.04 (0.02–0.06)	<0.001
ARV_{DBP}*	−0.02 (−0.04 to −0.001)	0.04
Model 4		
Mean DBP*	0.04 (0.02–0.06)	<0.001
SD_{DBP}*	−0.02 (−0.04 to −0.000002)	0.05

ARV, SD, and mean BP were calculated on the basis of visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. We included interaction terms for each BP parameter and interval (from visit 4 to visit 5; ie, 15 years). Adjusted βs (95% CIs) represent cognitive change associated with a 1-SD increase of each BP parameter over 15 years of follow-up (from visit 4 to visit 5). The 1-SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included the following: demographic variables (age at baseline, sex, race, education, apolipoprotein E ε4 alleles, and study center); clinical characteristics at visit 4 (body mass index, smoking, alcohol, total cholesterol, high-density lipoprotein, diabetes mellitus, use of antihypertensive drugs, and prevalent stroke); interval (from visit 4 to visit 5; ie, 15 years); mean SBP (in models 1 and 2) or mean DBP (in models 3 and 4) level; ARV_{SBP} (in model 1), SD_{SBP} (in model 2), ARV_{DBP} (in model 3), or SD_{DBP} (in model 4); and interval×ARV_{SBP} (result was shown in model 1), interval×SD_{SBP} (result was shown in model 2), interval×ARV_{DBP} (result was shown in model 3), or interval×SD_{DBP} (result was shown in model 4). Statistical significance was defined as $P<0.05$. ARV indicates average real variability; BP, blood pressure; CI, confidence interval; DBP, diastolic BP; SBP, systolic BP.
*Interaction terms for each BP parameter.

−0.004; $P>0.40$). A 1-SD higher mean DBP level was associated with a 0.04 increase in global cognitive *z* score from visit 4 to visit 5 (Table 3). When mean SBP and DBP levels were analyzed jointly, each yielded significant associations, with changes in global cognitive *z* score from visit 4 to visit 5 (standardized regression coefficient [95% confidence interval], −0.12 [−0.14 to −0.09] and 0.11 [0.09–0.14], respectively; all $P<0.001$). Cognitive task-specific analyses showed similar results (Table S7).

To quantify the association between mean SBP or DBP levels from visit 1 to visit 4 and cognitive decline from visit 4 to visit 5, participants were stratified into 9 groups using a 3×3 matrix of the tertiles of mean SBP and DBP levels (Figure 2). Table 3 shows that higher mean SBP and lower mean DBP levels were associated with a greater decline in global cognitive *z* score. Thus, the reference group was defined as the lowest tertile of SBP (≤114 mm Hg) and the highest tertile of DBP (≥76 mm Hg). Participants with SBP ≥128 mm Hg and DBP ≤67 mm Hg had a 0.43 decrease (95% confidence interval, −0.62 to −0.23; $P<0.001$) in global cognitive *z* score over 15 years compared with the reference group. The results obtained from subgroup analyses by the presence or absence of antihypertensive medication use at visit 4 were similar to those in the main analyses (Figures S1 and S2). Figure S3 shows the association between the tertiles of PP levels from visit 1 to visit 4 and cognitive decline from visit 4 to visit 5. Participants with PP ≥53 mm Hg had a 0.17 decrease (95% confidence interval, −0.22 to −0.13; $P<0.001$) in global cognitive *z* score over 15 years compared with participants with PP ≤43 mm Hg.

The magnitude of the effect of BP levels or variability from visit 1 to visit 4 on cognitive function at visit 4 or cognitive decline from visit 4 to visit 5 was similar after accounting for dropout and death using inverse-probability-of-attrition weighting methods (data not shown). There was no evidence

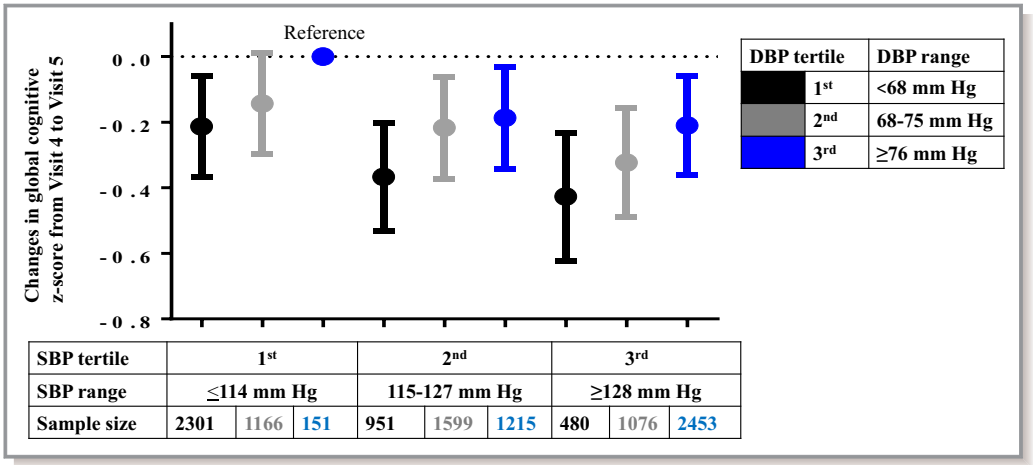

Figure 2. Associations between mean systolic blood pressure (SBP) or diastolic blood pressure (DBP) levels and cognitive decline. Participants were stratified into 9 groups using a 3×3 matrix of the tertiles of mean SBP and DBP levels from visit 1 to visit 4. Change in global cognitive *z* scores over 15 years (from visit 4 to visit 5) associated with each group is shown. The reference group was defined as participants who were classified into the first tertile of SBP and third tertile of DBP. Bars represent adjusted β (95% confidence interval) of the interaction term between each group and time interval (from visit 4 to visit 5; ie, 15 years). The models included demographic variables (age at baseline, sex, race, education, apolipoprotein E ε4 alleles, and study center)+clinical and behavioral characteristics at visit 4 (body mass index, smoking, alcohol, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, use of antihypertensive drugs, and prevalent stroke)+time interval+each group+interaction term between each group and time interval.

of interactions between each BP variability parameter and sex, race, apolipoprotein E ε4 allele, or antihypertensive medication use in association with changes in a global *z* score (all *P* interaction >0.18). The results obtained from subgroup analyses by sex, race, apolipoprotein E ε4 allele, and antihypertensive medication use were generally similar to those in the main analyses (Tables S12 through S20). Results were similar when excluding 225 participants who had a history of stroke at visit 4 (data not shown).

Discussion

In this biracial community-based cohort of middle-aged adults at baseline, higher long-term variability of SBP or DBP from visit 1 to visit 4 was concurrently and modestly associated with lower global cognition at visit 4 but not with cognitive change over a subsequent 15-year period (from visit 4 to visit 5). In contrast, higher mean SBP and lower mean DBP from visit 1 to visit 4 were each modestly associated with a greater decline in global cognition from visit 4 to visit 5. The group with mean SBP ≥115 mm Hg and/or DBP <68 mm Hg had greater cognitive decline than the group with SBP ≤114 mm Hg and DBP ≥76 mm Hg. No heterogeneity was observed in the association between long-term BP variability and cognition for sex, race, apolipoprotein E ε4 allele, or antihypertensive medication use.

Sabayan et al[13] reported that, among 5461 elderly participants (mean age, 75 years; 44% with vascular disease at baseline), higher SD_{SBP} and SD_{DBP} levels over 3 years of follow-up (13 visits) were associated with poorer performance in selective attention, processing speed, immediate verbal memory, and delayed memory. In another study, higher ARV_{SBP} from young adulthood to midlife (age, 25–50 years) was associated with worse psychomotor speed and verbal memory in midlife.[14] Cognitive function was assessed at a single time point in these studies, and, thus, it remains uncertain whether long-term BP variability is associated with cognitive change or merely indicative of concurrent lower cognitive function. We observed that higher long-term variability of SBP or DBP during midlife was modestly associated with lower cognitive function, yet not with cognitive decline. Although the results require careful interpretation because of potential underestimation of individual long-term BP variability defined over 4 clinic visits,[26] our results suggest that long-term BP variability may be an epiphenomenon of certain pathophysiological conditions.[22] For example, lower cognitive function could be a long-standing (preexisting) phenomenon among individuals who also have variable BP because of a disruption of homeostasis. A common cause may lead to both higher long-term SBP variability and lower cognitive function. For example, adverse stressors (eg, psychosocial stress and sleep deprivation), large-artery (aortic) stiffness, and lower socioeconomic status could lead to both increased long-term SBP variability and lower cognitive function.[19,20,28,29]

Higher midlife SBP levels have been consistently associated with lower cognitive function in later life.[1–11] Most studies have assessed cognitive function at a single time

point,[4–9] and, thus, our results have extended our understanding of this relationship by taking cognitive decline into account. In contrast, prior findings on the relationships between midlife DBP levels and late-life cognitive function have been inconsistent.[5,6,8,30] In a cohort of Swedish men (n=999), DBP ≥70 mm Hg (versus DBP <70 mm Hg) at the age of 50 years was associated with lower cognitive function at the age of 70 years.[6] In a Finnish cohort (n=1449; 62% women), no relationship was observed between DBP (≥90 versus <90 mm Hg) at ≈50 years of age and the presence of cognitive dysfunction 21 years later.[5] In contrast, analyses of data from a multiethnic cohort in the United Kingdom (n=1484) yielded a U-shaped association between low and high DBP measured at the age of 40 to 67 years and cognitive dysfunction 20 years later.[30] Middle age is a period when hemodynamic pattern alterations emerge: SBP increases continuously, whereas DBP tends to decline as a consequence of arterial stiffening.[31,32] Consequently, PP (SBP minus DBP) increases steeply after middle age. Therefore, characterization of individual DBP in midlife by a single measurement may be limited, and this might have contributed to the inconsistent results.[5,6,8,30] Indeed, a prior study from the ARIC Study demonstrated that higher DBP at visit 2 was associated with a steeper decline in global cognition from visit 2 to visit 5.[11] The inconsistency may be attributable to the definition of DBP (ie, we defined DBP on the basis of 4 clinic BP measurements [from visit 1 to visit 4 BPs] over 9 years). Therefore, lower DBP levels in our study may be indicative of DBP decrease from midlife on. Decreasing DBP from midlife to later life may be linked to cerebral hypoperfusion.[33,34] Decreasing DBP from midlife on is also a likely consequence of aortic stiffening, which contributes to cognitive decline.[29,35] We observed that the effect size of higher midlife PP levels on cognitive decline in later life was larger than that associated with higher SBP or with lower DBP. PP from midlife on is a measure of pulsatile pressure load and most representative of aortic stiffness.[31,32] The association between arterial stiffness and cognition has been reported.[11,36,37] The potential underlying mechanisms include the following: (1) excessive pulsatile mechanistic forces on the cerebrovasculature; (2) existing common pathways between arterial stiffness and cognition (eg, environmental and neurohormonal factors), inflammation, and oxidative stress[38]; and (3) impaired β amyloid clearance and τ-mediated neurodegeneration.[39,40]

Prehypertensive mean SBP levels (≥115 mm Hg) were associated with greater cognitive decline compared with optimal SBP levels (≤114 mm Hg). This association was exaggerated when prehypertensive mean SBP levels were accompanied by mean DBP levels <68 mm Hg. This suggests that maintaining optimal BP from midlife to later life, without reducing DBP to <68 mm Hg, may help to limit declines in cognition in later life. However, the BP range may be arbitrary and, thus, will need to be confirmed in randomized controlled trials. This will be clarified by the ongoing SPRINT-MIND (Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension Study),[41] which is testing the effects of lowering SBP to a target goal of <120 mm Hg, compared with <140 mm Hg, on incident dementia and cognitive decline in middle-aged and older adults with increased cardiovascular risk.

The major strengths of this study include long-term repeated measurements of office BP and cognitive function tests in a well-characterized cohort and application of a comprehensive standardized cognitive test battery. However, there are limitations. First, because this is an observational study, we are unable to determine causality in the findings. Second, the attrition arising from missing data attributable to death and hospitalization among those with higher SBP variability from midlife on is a potential bias. However, estimates of the associations between long-term SBP variability and cognitive decline appear to be similar in the inverse-probability-of-attrition weighting models. Third, although statistically significant, the effect sizes of long-term BP levels or variability on cognition appear to be small. Data from future ARIC Study examinations, including cognitive function measures, are needed to explore incident dementia in participants who had greater long-term BP levels or variability. Fourth, 28% of participants from the original ARIC Study cohort were not included in the present analysis. The included sample was slightly younger, had a lower proportion of blacks, and had higher educational attainment than those excluded. Therefore, the included participants might have a lower risk of cognitive decline. Fifth, cognitive reserve, which is determined by lifetime exposures, including occupational attainment and physical and leisure activities, may contribute to individual differences in age-related cognitive changes.[42,43] Possible residual confounding, including occupational attainment and physical activity, may be affecting the associations of BP levels or variability with cognition. Sixth, we did not exclude participants who were diagnosed with dementia during follow-up, which potentially affects the association between visit-to-visit BP variability and cognition. Seventh, our sample consists of blacks and whites; thus, our findings cannot be generalized to other race/ethnic groups.

This study illustrates the associations of long-term BP levels and variability during midlife with late-life cognition. Assessment of long-term BP variability may be useful in identifying individuals with lower cognitive function. Unraveling the underlying mechanisms of higher long-term BP variability (eg, psychosocial stress and aortic stiffness) may provide new prophylactic therapies for preventing or slowing cognitive decline. Furthermore, we highlight a potential effect of prehypertensive mean SBP levels and lower DBP levels from midlife to later life on subsequent cognitive decline. This hypothesis will need to be confirmed by interventional trials.

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Disclosures

None.

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Supplemental Material

Table S1. Associations between SD_{BP} and CV_{BP} in 11,408 participants.

Variables	SD_{SBP}, mmHg	SD_{DBP}, mmHg
CV_{SBP}, mmHg	**0.97***	**0.42***
CV_{DBP}, mmHg	**0.38***	**0.96***

Pearson's correlation coefficients are shown. Statistical significance was defined as $p<0.05$.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; SD; standard deviation, CV; coefficient of variation. * $p<0.0001$.

Table S2. Comparison of clinical characteristics of participants who were included in the current study and those who were not included, ARIC.

Descriptive variable at visit 1	Included (n=11,408)	Not included (n=4,384)	p-value
Age, years	54.3±5.7	55.6±5.9	<0.001
Men, %	44	47	<0.001
Blacks, %	21	42	<0.001
Educational level, %			
<High school	18	40	
High school	43	36	<0.001
College	39	25	
Body mass index, kg/m^2	27.5±5.1	28.3±6.0	<0.001
Current smoker, %	21	39	<0.001
Current drinker, %	59	47	<0.001
Antihypertensive medication, %	27	40	<0.001
SBP, mmHg	119.4±17.2	126.6±22.1	<0.001
DBP, mmHg	73.1±10.6	75.4±12.9	<0.001
Total cholesterol, mg/dL	214.5±41.1	216.4±44.6	0.07
High-density lipoprotein, mg/dL	52.1±17.0	50.3±17.4	<0.001
Diabetes mellitus, %	7	18	<0.001
APOE ε4 alleles			
0	69	67	
1	28	30	0.01
2	3	3	

Data are expressed as the means ± SD or percentage. p-values were obtained by an unpaired t-test or chi-squared test.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; APO E, apolipoprotein E.

Table S3. The mean+SD of SBP and DBP levels and variability (n=11,408).

Variables	
Mean BP levels from Visit 1 to Visit 4	
Mean SBP levels	122.7±15.4
Mean DBP levels	71.9±8.6
BP variability from Visit 1 to Visit 4	
SD_{SBP}, mmHg	10.1±5.9
SD_{DBP}, mmHg	5.8±3.2
ARV_{SBP}, mmHg	11.1±6.8
ARV_{DBP}, mmHg	6.6±3.8

Data are expressed as the means ± SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; SD, standard deviation, ARV, average real variability.

Table S4. Associations between long-term BP levels or variability and demographic variables and clinical characteristics (n=11,408).

	Long-term BP parameters					
Variables	**ARV_{SBP}**	**ARV_{DBP}**	**SD_{SBP}**	**SD_{DBP}**	**Mean SBP levels**	**Mean DBP levels**
Clinical characteristics at Visit 1						
Age, years	**0.13**‡	**0.04**‡	**0.13**‡	**0.05**‡	**0.26**‡	**-0.12**‡
Body mass index, kg/m^2	**0.11**‡	**0.09**‡	**0.09**‡	**0.12**‡	**0.25**‡	**0.21**‡
Total cholesterol, mg/dL	**0.06**‡	**0.05**‡	**0.06**‡	**0.06**‡	**0.10**‡	0.018
High-density lipoprotein, mg/dL	-0.02	**-0.04**‡	-0.01	**-0.06**‡	**-0.07**‡	**-0.06**‡
BP parameters						
SBP at Visit 1, mmHg	**0.33**‡	**0.25**‡	**0.27**‡	**0.32**‡	**0.84**‡	**0.54**‡
DBP at Visit 1, mmHg	**0.22**‡	**0.22**‡	**0.18**‡	**0.29**‡	**0.57**‡	**0.83**‡
Long-term BP levels or variability						
SD_{SBP}, mmHg	**0.87**‡	**0.40**‡	**-**	**0.45**‡	**0.46**‡	**0.25**‡
SD_{DBP}, mmHg	**0.44**‡	**0.86**‡	**0.45**‡	**-**	**0.26**‡	**0.18**‡
ARV_{SBP}, mmHg	**-**	**0.47**‡	**0.87**‡	**0.44**‡	**0.43**‡	**0.22**‡
ARV_{DBP}, mmHg	**0.47**‡	**-**	**0.40**‡	**0.86**‡	**0.23**‡	**0.16**‡
Mean SBP levels from Visit 1 to Visit 4, mmHg	**0.43**‡	**0.23**‡	**0.46**‡	**0.26**‡	**-**	**0.63**‡
Mean DBP levels from Visit 1 to Visit 4, mmHg	**0.22**‡	**0.16**‡	**0.25**‡	**0.18**‡	**0.63**‡	**-**

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. Pearson's correlation coefficients are shown. Statistical significance was defined as $p<0.05$. * $p<0.05$; † $p<0.01$; ‡ $p<0.001$.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation, ARV, average real variability.

Table S5. The differences of long-term BP levels or variability by clinical characteristics (n=11,408)												
	ARV_{SBP}	**p-value**	**ARV_{DBP}**	**p-value**	**SD_{SBP}**	**p-value**	**SD_{DBP}**	**p-value**	**Mean SBP levels**	**p-value**	**Mean DBP levels**	**p-value**
Sex												
Men	10.7±6.7	<0.001	6.7±3.83	0.02	10.7±6.7	<0.001	5.9±3.2	0.03	123.2±14.6	<0.001	73.5±8.5	<0.001
Women	11.4±7.0		6.5±3.7		11.4±7.0		5.7±3.2		122.3±16.0		70.7±8.5	
Race												
White individuals	10.6±6.4	<0.001	6.3±3.6	<0.001	10.6±6.4	<0.001	5.6±3.1	<0.001	121.1±14.9	<0.001	70.7±8.2	<0.001
Black individuals	13.3±8.2		7.5±4.2		13.3±8.2		6.6±3.6		128.5±15.7		76.6±8.7	
Educational attainment												
< High School	12.5±7.6	<0.001	7.0±4.0	<0.001	12.5±7.6	<0.001	6.2±3.4	<0.001	126.8±15.7	<0.001	72.6± 9.1	<0.001
High School	11.1±6.7		6.5± 3.7		11.1±6.7		5.8±3.2		122.53±15.2		71.6±8.5	
College	10.6±6.5		6.4±3.7		10.6±6.5		5.6± 3.1		120.9±15.1		72.1±8.6	
Current smoking at Visit 1												
Yes	11.6±7.0	<0.001	6.9±3.9	<0.001	10.6±6.1	<0.001	6.0±3.2	<0.001	120.2±15.4	<0.001	70.1±9.1	<0.001
No	11.0±6.8		6.5± 3.7		9.9±5.8		5.7±3.2		123.4±15.3		72.5± 8.4	
Daily drinking at Visit 1												
Yes	10.6±6.4	<0.001	6.4±3.6	<0.001	9.6±5.5	<0.001	5.6±3.1	<0.001	121.4±15.0	<0.001	71.9±8.5	0.62
No	11.9±7.4		6.9±3.9		10.7± 6.3		6.0±3.3		124.4±15.8		72.0±8.8	
Antihypertensive medication use at Visit 1												
Yes	13.5±8.1	<0.001	7.4±4.2	<0.001	12.1±6.8	<0.001	6.6±3.6	<0.001	129.6±15.7	<0.001	74.3±8.9	<0.001
No	10/3±6.1		6.2±3.5		9.3±5.3		5.5±3.0		120.1±14.4		71.1±8.4	
Diabetes mellitus at Visit 1												
Yes	13.7±8.5	<0.001	7.5±4.1	<0.001	12.1±7.0	<0.001	6.8± 3.6	<0.001	129.8±15.4	<0.001	71.4±8.4	0.04
No	10.9±6.7		6.5±3.7		9.9±5.7		5.7±3.1		122.1±15.2		72.0±8.6	
APOE ε4 alleles												
0	11.1±6.7	0.71	6.6± 3.8	0.99	10.0±5.8	0.23	5.8±3.2	0.45	122.6±15.3	0.01	71.9± 8.5	0.14
1	11.3±7.1		6.6±3.8		10.2±6.0		5.8±3.2		122.6±15.5		72.1±9.0	
2	11.7±7.6		6.7±4.3		10.8±6.7		6.0±3.4		125.5±16.2		73.0±9.0	
P values were obtained by the unpaired t-test or analysis of variance. Statistical significance was defined as p<0.05.												

Table S6. Cognitive change from Visit 4 to Visit 5 (n=11,408).

Descriptive variable	Visit 4	Visit 5	p-value
Cognitive test score			
Global *z* score	-0.02±1.0	-0.6±1.0	<0.001
DWRT, No. of words	6.6±1.6	5.2±1.9	<0.001
DWRT, *z* score	-0.03±1.1	-0.9±1.3	<0.001
DSST, No. of symbols	43.7±13.4	37.9±12.0	<0.001
DSST, *z* score	-0.1±0.9	-0.5±0.9	<0.001
WFT, No. of words	33.5±12.5	32.8±12.4	<0.001
WFT, *z* score	0.03±1.0	-0.03±1.0	<0.001

Data are expressed as the means ± SD. p-values were obtained by an unpaired t-test. Statistical significance was defined as $p<0.05$.

DWRT, indicates delayed word recall test; DSST, digit symbol substitution test; WRT, word fluency test.

Table S7. Associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive function at Visit 4 (n=11,408).

	DWRT *z* score		**DSST *z* score**		**WFT *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:						
Mean SBP	0.02 (-0.01 to 0.04)	0.19	-0.01 (-0.02 to 0.01)	0.44	-0.01 (-0.03 to 0.01)	0.56
ARV_{SBP}	**-0.03 (-0.05 to -0.01)**	0.01	**-0.03 (-0.04 to -0.01)**	<0.001	-0.01 (-0.02 to 0.01)	0.55
Model 2:						
Mean SBP	0.02(-0.003 to 0.04)	0.08	-0.01 (-0.03 to 0.01)	0.24	-0.004 (-0.03 to 0.02)	0.72
SD_{SBP}	**-0.04(-0.06 to -0.01)**	<0.01	**-0.02 (-0.04 to -0.01)**	<0.01	-0.01 (-0.03 to 0.01)	0.17
Model 3:						
Mean DBP	-0.01 (-0.03 to 0.01)	0.28	-0.01 (-0.03 to 0.002)	0.09	-0.004 (-0.02 to 0.02)	0.72
ARV_{DBP}	-0.01 (-0.03 to 0.01)	0.32	**-0.02 (-0.04 to -0.01)**	<0.01	-0.01 (-0.03 to 0.01)	0.30
Model 4:						
Mean DBP	-0.01 (-0.03 to 0.01)	0.34	-0.01 (-0.03 to 0.002)	0.10	-0.003 (-0.02 to 0.02)	0.76
SD_{DBP}	**-0.03 (-0.05 to -0.01)**	<0.01	**-0.03 (-0.05 to -0.02)**	<0.001	**-0.03 (-0.04 to -0.01)**	<0.01

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. Adjusted βs (95% CIs) associated with 1 SD increases of each BP parameter are shown. 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg.

Models included: demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (results were shown in models 1 and 2) or mean DBP levels (results were shown in models 3 and 4); ARV_{SBP} (result was shown in model 1) or SD_{SBP} (result was shown in model 2) or ARV_{DBP} (result was shown in model 3) or SD_{DBP} (result was shown in model 4); time interval×mean SBP levels (in models 1 and 2) or DBP levels (in models 3 and 4); time interval×ARV_{SBP} (in model 1) or time interval×SD_{SBP} (in model 2) or time interval×ARV_{DBP} (in model 3) or time interval×SD_{DBP} (in model 4). Statistical significance was defined as P <0.05.

DWRT indicates Delayed Word Recall Test; DSST, Digit Symbol Substitution Test; WFT, Word Fluency Test. Statistical significance was defined as p<0.05.

Table S8. Associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive change from Visit 4 to Visit 5 (n=11,408).

	DWRT *z* score		**DSST *z* score**		**WFT *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:						
Mean SBP*	**-0.04 (-0.08 to -0.01)**	0.02	**-0.02 (-0.04 to -0.002)**	0.03	**-0.04 (-0.06 to -0.02)**	<0.01
ARV_{SBP}*	0.03 (-0.01 to 0.07)	0.11	-0.003 (-0.02 to 0.01)	0.71	-0.10 (-0.03 to 0.01)	0.46
Model 2:						
Mean SBP*	**-0.05 (-0.09 to -0.01)**	0.01	-0.02 (-0.03 to 0.001)	0.07	**-0.04 (-0.06 to -0.02)**	<0.001
SD_{SBP}*	0.03(-0.01 to 0.07)	0.13	-0.004 (-0.02 to 0.01)	0.68	0.01 (-0.02 to 0.03)	0.63
Model 3:						
Mean DBP*	**0.04 (0.01 to 0.07)**	0.02	**0.04 (0.02 to 0.05)**	<0.001	0.01 (-0.01 to 0.03)	0.34
ARV_{DBP}*	-0.002 (-0.03 to 0.03)	0.93	-0.01 (-0.03 to 0.002)	0.09	**-0.03 (-0.05 to -0.02)**	<0.001
Model 4:						
Mean DBP*	**0.04 (0.01 to 0.07)**	0.02	**0.04 (0.03 to 0.06)**	<0.001	0.01 (-0.01 to 0.03)	0.35
SD_{DBP}*	-0.01 (-0.04 to 0.03)	0.93	-0.01 (-0.03 to 0.002)	0.08	-0.03 (-0.05 to -0.01)	0.07

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. We included interaction terms for each BP parameter (marked with asterisks) and time interval (from Visit 4 to Visit 5; i.e., 15 years) in associations with cognitive change from Visit 4 to Visit 5. Adjusted βs (95% CIs) therefore represent cognitive change associated with a 1-SD increase of each BP parameter over 15 years of follow-up (from Visit 4 to Visit 5). 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg.

Models included: demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (models 1 and 2) or mean DBP levels (models 3 and 4); ARV_{SBP} (model 1) or SD_{SBP} (model 2) or ARV_{DBP} (model 3) or SD_{DBP} (model 4); time interval×mean SBP levels (results were shown in models 1 and 2) or time interval×DBP levels (results were shown in models 3 and 4); time interval×ARV_{SBP} (result was shown in model 1) or time interval×SD_{SBP} (result was shown in model 2) or time interval×ARV_{DBP} (result was shown in model 3) or time interval×SD_{DBP} (result was shown in model 4). Statistical significance was defined as $p<0.05$.

Table S9. Associations between long-term PP levels or variability from Visit 1 to Visit 4 and cognitive function at Visit 4 (n=11,408)

	Global *z* score change		**DWRT *z* score change**		**DSST *z* score change**		**WFT *z* score change**	
Variables	**β(SE)**	**p-value**	**β(SE)**	**p-value**	**β(SE)**	**p-value**	**β(SE)**	**p-value**
Model 1:								
Mean PP	0.009 (0.01)	0.36	**0.03 (0.01)**	0.01	0.0004 (0.01)	0.96	-0.008 (0.01)	0.47
ARV_{PP}	**-0.03 (0.01)**	<0.001	**-0.04 (0.01)**	<0.01	**-0.03 (0.01)**	<0.01	-0.002 (0.01)	0.98
Model 2:								
Mean PP	0.008 (0.01)	0.40	**0.04 (0.01)**	<0.01	-0.005 (0.01)	0.57	-0.01 (0.01)	0.39
SD_{PP}	**-0.03 (0.01)**	<0.01	**-0.04 (0.01)**	<0.001	**-0.02 (0.01)**	0.01	0.002 (0.01)	0.82

PP=pulse pressure. ARV_{PP}, SD_{PP}, and mean pulse pressure were calculated based upon Visit 1, 2, 3, and 4 SBP and DBP. β means standardized regression coefficient. Adjusted βs (95% CIs) associated with 1 SD increases of each BP parameter are shown. 1 SD increases of each BP parameter are as follows: ARV_{pp}, per 4.8 mm Hg; SD_{PP}, per 5.3 mm Hg; mean PP, per 12.0 mm Hg. Models included; demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean PP levels (results were shown in models 1 and 2); ARV_{PP} (result was shown in model 1) or SD_{PP} (result was shown in model 2); time interval×mean PP levels (in models 1 and 2); time interval×ARV_{PP} (in model 1) or SD_{PP} (in model 2). Statistical significance was defined as $p<0.05$.

Table S10. Associations between long-term PP levels or variability from Visit 1 to Visit 4 and cognitive change from Visit 4 to Visit 5 (n=11,408).

	Global *z* score change		**DWRT *z* score change**		**DSST *z* score change**		**WFT *z* score change**	
Variables	**β(SE)**	**p-value**	**β(SE)**	**p-value**	**β(SE)**	**p-value**	**β(SE)**	**p-value**
Model 1:								
Mean PP*	**-0.09(0.01)**	<0.001	**-0.10(0.02)**	<0.001	**-0.06(0.01)**	<0.001	**-0.05(0.01)**	<0.001
ARV_{PP}*	0.01(0.01)	0.38	**0.04(0.002)**	0.04	0.004(0.01)	0.67	-0.02(0.01)	0.16
Model 2:								
Mean PP*	**-0.09(0.01)**	<0.001	**-0.10(0.02)**	<0.001	**-0.06(0.01)**	<0.001	**-0.05(0.01)**	<0.001
SD_{PP}*	0.003(0.01)	0.78	0.03(0.02)	0.10	-0.01(0.10)	0.57	**-0.02(0.01)**	0.04

PP=pulse pressure. ARV_{PP}, SD_{PP}, and mean pulse pressure were calculated based upon Visit 1, 2, 3, and 4 SBP and DBP. β means standardized regression coefficient. We included interaction terms for each BP parameter (marked with asterisks) and time interval (from Visit 4 to Visit 5; i.e., 15 years) in associations with cognitive change from Visit 4 to Visit 5. Adjusted βs (95% CIs) therefore represent cognitive change associated with a 1-SD increase of each BP parameter over 15 years of follow-up (from Visit 4 to Visit 5). 1 SD increases of each BP parameter are as follows: ARV_{pp}, per 4.8 mm Hg; SD_{PP}, per 5.3 mm Hg; mean PP, per 12.0 mm Hg. Models included; demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke)+time interval (from Visit 4 to Visit 5; i.e., 15 years); mean PP levels; ARV_{PP} (in model 1) or SD_{PP} (in model 2); time interval×mean PP levels (results were shown in models 1 and 2); time interval×ARV_{PP} (result was shown in model 1) or SD_{PP} (result was shown in model 2). Statistical significance was defined as $p<0.05$.

Table S11. Associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive function at Visit 4 (n=11,408).

	Global *z* score	
Variables	**β (95% CIs)**	**p-value**
Model 1:		
Mean SBP	**-0.02 (-0.04 to -0.002)**	0.03
VIM_{SBP}	**-0.03 (-0.04 to -0.01)**	<0.01
Model 2:		
Mean DBP	-0.003 (-0.02 to 0.01)	0.69
VIM_{DBP}	**-0.04 (-0.06 to -0.03)**	<0.001

VIM and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. Adjusted βs (95% CIs) associated with 1 SD increases of each BP parameter are shown. 1 SD increases of each BP parameter are as follows: VIM_{SBP}, per 4.99 unit and VIM_{DBP}, per 3.14 unit. Models included: demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center) + clinical characteristics at visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke)+interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (results were shown in model 1) or mean DBP levels (results were shown in model 2); VIM_{SBP} (result was shown in model 1) or VIM_{DBP} (result was shown in model 2); interval×mean SBP (in model 1) or interval×DBP (in model2) levels; interval×VIM_{SBP} (in model 1) or interval×VIM_{DBP} (in model 2). Statistical significance was defined as $p<0.05$.

Table S12. Associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive change from Visit 4 to Visit 5 (n=11,408).

	Global *z* score	
Variables	**β (95% CIs)**	**p-value**
Model 1:		
Mean SBP*	**-0.04 (-0.06 to -0.02)**	<0.001
VIM_{SBP}*	0.003 (-0.02 to 0.02)	0.81
Model 2:		
Mean DBP*	**0.04 (0.02 to 0.06)**	<0.001
VIM_{DBP}*	**-0.02 (-0.04 to -0.001)**	0.04

VIM and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. We included interaction terms for each BP parameter (marked with asterisk) and interval (from Visit 4 to Visit 5; i.e., 15 years). Adjusted βs (95% CIs) therefore represent cognitive change associated with a 1-SD increase of each BP parameter over 15-years follow-up (from Visit 4 to Visit 5). 1 SD increases of each BP parameter are as follows: VIM_{SBP}, per 4.99 unit and VIM_{DBP}, per 3.14 unit. Models included: demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center); clinical characteristics at visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (in model 1) or DBP (in model 2) levels; VIM_{SBP} (in model 1) or VIM_{DBP} (in model 2); time interval×VIM_{SBP} (result was shown in model 1) or time interval×VIM_{DBP} (result was shown in model 2). Statistical significance was defined as $p<0.05$.

Table S13. Sex-specific associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive function at Visit 4.

	Men (n=5,006)		**Women (n=6,402)**	
	Global *z* score		**Global *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:				
Mean SBP	0.02 (-0.01 to 0.04)	0.29	-0.01 (-0.04 to 0.01)	0.27
ARV_{SBP}	**-0.03 (-0.06 to -0.01)**	0.02	-0.02 (-0.04 to 0.002)	0.07
Model 2:				
Mean SBP	0.02 (-0.01 to 0.05)	0.21	-0.01 (-0.04 to 0.01)	0.33
SD_{SBP}	**-0.04 (-0.07 to -0.01)**	<0.01	**-0.03 (-0.05 to -0.003)**	0.03
Model 3:				
Mean DBP	0.003 (-0.02 to 0.03)	0.81	**-0.03 (-0.05 to -0.01)**	0.02
ARV_{DBP}	-0.004 (-0.03 to 0.20)	0.76	**-0.03 (-0.05 to -0.01)**	<0.01
Model 4:				
Mean DBP	0.005 (-0.02 to 0.03)	0.72	**-0.03 (-0.05 to -0.01)**	0.02
SD_{DBP}	**-0.03 (-0.05 to -0.005)**	0.02	**-0.05 (-0.07 to -0.03)**	<0.001

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. Adjusted βs (95% CIs) associated with 1 SD increases of each BP parameter are shown. 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included: demographic variables (age at baseline, race, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (results were shown in models 1 and 2) or mean DBP levels (results were shown in models 3 and 4); ARV_{SBP} (result was shown in model 1) or SD_{SBP} (result was shown in model 2) or ARV_{DBP} (result was shown in model 3) or SD_{DBP} (result was shown in model 4); time interval×mean SBP levels (in models 1 and 2) or time interval×DBP levels (in models 3 and 4); time interval×ARV_{SBP} (in model 1) or time interval×SD_{SBP} (in model 2) or time interval×ARV_{DBP} (in model 3) or time interval×SD_{DBP} (in model 4). Statistical significance was defined as $p<0.05$.

Table S14. Sex-specific associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive change from Visit 4 to Visit 5

	Men (n=5,006)		**Women (n=6,402)**	
	Global *z* score		**Global *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:				
Mean SBP*	-0.04 (-0.07 to 0.001)	0.06	**-0.04 (-0.07 to -0.01)**	<0.01
ARV_{SBP}*	-0.01 (-0.05 to 0.02)	0.50	0.01 (-0.02 to 0.04)	0.42
Model 2:				
Mean SBP*	**-0.04 (-0.08 to -0.003)**	0.04	**-0.04 (-0.07 to -0.02)**	<0.01
SD_{SBP}*	-0.01(-0.04 to 0.03)	0.73	0.02 (-0.01 to 0.05)	0.24
Model 3:				
Mean DBP*	0.03 (-0.002 to 0.07)	0.06	**0.05 (0.02 to 0.08)**	<0.001
ARV_{DBP}*	**-0.05 (-0.08 to -0.02)**	<0.01	0.001 (-0.03 to 0.03)	0.96
Model 4:				
Mean DBP*	0.03 (0.001 to0.07)	0.05	**0.05 (0.02 to 0.07)**	<0.001
SD_{DBP}*	**-0.06 (-0.09 to -0.02)**	<0.01	0.003 (-0.02 to 0.03)	0.85

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. We included interaction terms for each BP parameter (marked with asterisks) and time interval (from Visit 4 to Visit 5; i.e., 15 years) in associations with cognitive change from Visit 4 to Visit 5. Adjusted βs (95% CIs) therefore represent cognitive change associated with a 1-SD increase of each BP parameter over 15 years of follow-up (from Visit 4 to Visit 5). 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included: demographic variables (age at baseline, race, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (models 1 and 2) or mean DBP levels (models 3 and 4); ARV_{SBP} (model 1) or SD_{SBP} (model 2) or ARV_{DBP} (model 3) or SD_{DBP} (model 4); time interval×mean SBP levels (results were shown in models 1 and 2) or time interval×DBP levels (results were shown in models 3 and 4); time interval×ARV_{SBP} (result was shown in model 1) or time interval×SD_{SBP} (result was shown in model 2) or time interval×ARV_{DBP} (result was shown in model 3) or time interval×SD_{DBP} (result was shown in model 4). Statistical significance was defined as $p<0.05$.

Table S15. Race-specific associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive function at Visit 4.

	Blacks (n=2,403)		**Whites (n=9,005)**	
	Global *z* score		**Global *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:				
Mean SBP	-0.02 (-0.07 to 0.02)	0.24	0.01 (-0.01 to 0.03)	0.34
ARV_{SBP}	-0.02 (-0.06 to 0.10)	0.12	**-0.02 (-0.04 to -0.004)**	0.045
Model 2:				
Mean SBP	-0.03 (-0.07 to -0.01)	0.15	0.01 (-0.01 to 0.04)	0.16
SD_{SBP}	-0.02 (-0.06 to -0.01)	0.16	**-0.03 (-0.05 to -0.01)**	<0.01
Model 3:				
Mean DBP	-0.02 (-0.06 to 0.02)	0.33	-0.002 (-0.02 to 0.02)	0.87
ARV_{DBP}	-0.03 (-0.06 to 0.004)	0.08	-0.01 (-0.03 to 0.006)	0.20
Model 4:				
Mean DBP	-0.02 (-0.06 to 0.02)	0.29	0.001 (-0.02 to 0.02)	0.95
SD_{DBP}	**-0.05 (-0.08 to -0.02)**	<0.01	**-0.03 (-0.05 to -0.01)**	<0.01

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. Adjusted βs (95% CIs) associated with 1 SD increases of each BP parameter are shown. 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included: demographic variables (age at baseline, sex, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (results were shown in models 1 and 2) or mean DBP levels (results were shown in models 3 and 4); ARV_{SBP} (result was shown in model 1) or SD_{SBP} (result was shown in model 2) or ARV_{DBP} (result was shown in model 3) or SD_{DBP} (result was shown in model 4); time interval×mean SBP levels (in models 1 and 2) or time interval×DBP levels (in models 3 and 4); time interval×ARV_{SBP} (in model 1) or time interval×SD_{SBP} (in model 2) or time interval×ARV_{DBP} (in model 3) or time interval×SD_{DBP} (in model 4). Statistical significance was defined as $p<0.05$.

Table S16. Race-specific associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive change from Visit 4 to Visit 5

	Blacks (n=2,403)		**Whites (n=9,005)**	
	Global *z* score		**Global *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:				
Mean SBP*	-0.03 (-0.08 to 0.02)	0.25	**-0.06 (-0.09 to -0.04)**	<0.001
ARV_{SBP}*	-0.01 (-0.05 to 0.03)	0.66	-0.01 (-0.03 to 0.02)	0.66
Model 2:				
Mean SBP*	-0.04 (-0.09 to 0.01)	0.15	**-0.07 (-0.09 to -0.04)**	<0.001
SD_{SBP}*	0.01 (-0.04 to 0.05)	0.71	-0.01 (-0.03 to 0.02)	0.65
Model 3:				
Mean DBP*	0.03 (-0.03 to 0.08)	0.29	0.02 (-0.01 to 0.04)	0.17
ARV_{DBP}*	-0.01 (-0.05 to 0.03)	0.70	**-0.04 (-0.06 to -0.01)**	<0.01
Model 4:				
Mean DBP*	0.02 (-0.03 to 0.07)	0.35	0.01 (-0.01 to 0.04)	0.20
SD_{DBP}*	0.004 (-0.04 to 0.05)	0.85	**-0.04 (-0.07 to -0.02)**	<0.01

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. We included interaction terms for each BP parameter (marked with asterisks) and time interval (from Visit 4 to Visit 5; i.e., 15 years) in associations with cognitive change from Visit 4 to Visit 5. Adjusted βs (95% CIs) therefore represent cognitive change associated with a 1-SD increase of each BP parameter over 15 years of follow-up (from Visit 4 to Visit 5). 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included: demographic variables (age at baseline, sex, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (models 1 and 2) or mean DBP levels (models 3 and 4); ARV_{SBP} (model 1) or SD_{SBP} (model 2) or ARV_{DBP} (model 3) or SD_{DBP} (model 4); time interval×mean SBP levels (results were shown in models 1 and 2) or time interval×DBP levels (results were shown in models 3 and 4); time interval×ARV_{SBP} (result was shown in model 1) or time interval×SD_{SBP} (result was shown in model 2) or time interval×ARV_{DBP} (result was shown in model 3) or time interval×SD_{DBP} (result was shown in model 4). Statistical significance was defined as $p<0.05$.

Table S17. Associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive function at Visit 4 by the presence or absence of antihypertensive medication use at Visit 4.

	Antihypertensive medication use (-), n=5,537		**Antihypertensive medication use (+), n=5,871**	
	Global *z* score		**Global *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:				
Mean SBP	0.02 (-0.01 to 0.04)	0.20	-0.01 (-0.04 to 0.01)	0.31
ARV_{SBP}	**-0.03 (-0.06 to -0.003)**	0.03	-0.02 (-0.04 to 0.001)	0.06
Model 2:				
Mean SBP	0.02 (-0.01 to 0.05)	0.15	-0.01 (-0.04 to 0.01)	0.42
SD_{SBP}	**-0.03 (-0.06 to -0.004)**	0.02	**-0.03 (-0.05 to -0.01)**	0.01
Model 3:				
Mean DBP	-0.002 (-0.03 to 0.02)	0.89	-0.02 (-0.05 to 0.002)	0.07
ARV_{DBP}	-0.02 (-0.04 to 0.01)	0.17	**-0.02 (-0.04 to -0.001)**	0.04
Model 4:				
Mean DBP	-0.001 (-0.03 to 0.02)	0.96	-0.02 (-0.04 to 0.004)	0.10
SD_{DBP}	**-0.04 (-0.06 to -0.01)**	<0.01	**-0.04 (-0.06 to -0.02)**	<0.001

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. Adjusted βs (95% CIs) associated with 1 SD increases of each BP parameter are shown. 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included: demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (results were shown in models 1 and 2) or mean DBP levels (results were shown in models 3 and 4); ARV_{SBP} (result was shown in model 1) or SD_{SBP} (result was shown in model 2) or ARV_{DBP} (result was shown in model 3) or SD_{DBP} (result was shown in model 4); time interval×mean SBP levels (in models 1 and 2) or time interval×DBP levels (in models 3 and 4); time interval×ARV_{SBP} (in model 1) or time interval×SD_{SBP} (in model 2) or time interval×ARV_{DBP} (in model 3) or time interval×SD_{DBP} (in model 4). Statistical significance was defined as $p<0.05$.

Table S18. Associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive change from Visit 4 to Visit 5 by the presence or absence of antihypertensive medication use at Visit 4.

	Antihypertensive medication use (-), n=5,537		**Antihypertensive medication use (+), n=5,871**	
	Global *z* score		**Global *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:				
Mean SBP*	**-0.05 (-0.09 to -0.02)**	<0.01	-0.02(-0.06 to 0.01)	0.21
ARV_{SBP}*	-0.02 (-0.06 to 0.02)	0.45	0.01 (-0.02 to 0.04)	0.44
Model 2:				
Mean SBP*	**-0.06 (-0.09 to -0.02)**	<0.01	-0.03 (-0.06 to 0.002)	0.07
SD_{SBP}*	-0.005 (-0.04 to 0.003)	0.80	0.02 (-0.01 to 0.05)	0.26
Model 3:				
Mean DBP*	**0.04 (0.01 to 0.07)**	<0.01	**0.05 (0.02 to 0.08)**	<0.01
ARV_{DBP}*	**-0.03 (-0.06 to -0.002)**	0.04	-0.005 (-0.03 to 0.02)	0.74
Model 4:				
Mean DBP*	**0.04 (0.01 to 0.07)**	<0.01	**0.05 (0.02 to 0.08)**	<0.01
SD_{DBP}*	-0.03 (-0.06 to 0.005)	0.09	-0.01 (-0.04 to 0.02)	0.54

ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. We included interaction terms for each BP parameter (marked with asterisks) and time interval (from Visit 4 to Visit 5; i.e., 15 years) in associations with cognitive change from Visit 4 to Visit 5. Adjusted βs (95% CIs) therefore represent cognitive change associated with a 1-SD increase of each BP parameter over 15 years of follow-up (from Visit 4 to Visit 5). 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg Models included: demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (models 1 and 2) or mean DBP levels (models 3 and 4); ARV_{SBP} (model 1) or SD_{SBP} (model 2) or ARV_{DBP} (model 3) or SD_{DBP} (model 4); time interval×mean SBP levels (results were shown in models 1 and 2) or time interval×DBP levels (results were shown in models 3 and 4); time interval×ARV_{SBP} (result was shown in model 1) or time interval×SD_{SBP} (result was shown in model 2) or time interval×ARV_{DBP} (result was shown in model 3) or time interval×SD_{DBP} (result was shown in model 4). Statistical significance was defined as $p<0.05$.

Table S19. Associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive function at Visit 4 according to ApoE ε4 alleles.

	ApoE ε4 alleles (0), n=7,637		**ApoE ε4 alleles (≥1), n=3,771**	
	Global *z* score		**Global *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:				
Mean SBP	0.01 (-0.01 to 0.03)	0.52	-0.02 (-0.05 to 0.02)	0.29
ARV_{SBP}	**-0.03 (-0.05 to -0.01)**	<0.01	-0.01 (-0.04 to 0.02)	0.48
Model 2:				
Mean SBP	0.001 (-0.01 to 0.03)	0.45	-0.02 (-0.05 to 0.02)	0.36
SD_{SBP}	**-0.04 (-0.06 to -0.02)**	<0.001	-0.02 (-0.05 to 0.01)	0.24
Model 3:				
Mean DBP	-0.005 (-0.03 to 0.02)	0.65	**-0.03 (-0.06 to -0.001)**	0.04
ARV_{DBP}	**-0.02 (-0.04 to -0.002)**	0.03	-0.10 (-0.04 to 0.02)	0.48
Model 4:				
Mean DBP	-0.002 (-0.02 to 0.02)	0.82	**-0.03 (-0.06 to -0.005)**	0.02
SD_{DBP}	**-0.04 (-0.06 to -0.02)**	<0.001	-0.03 (-0.06 to 0.005)	0.10

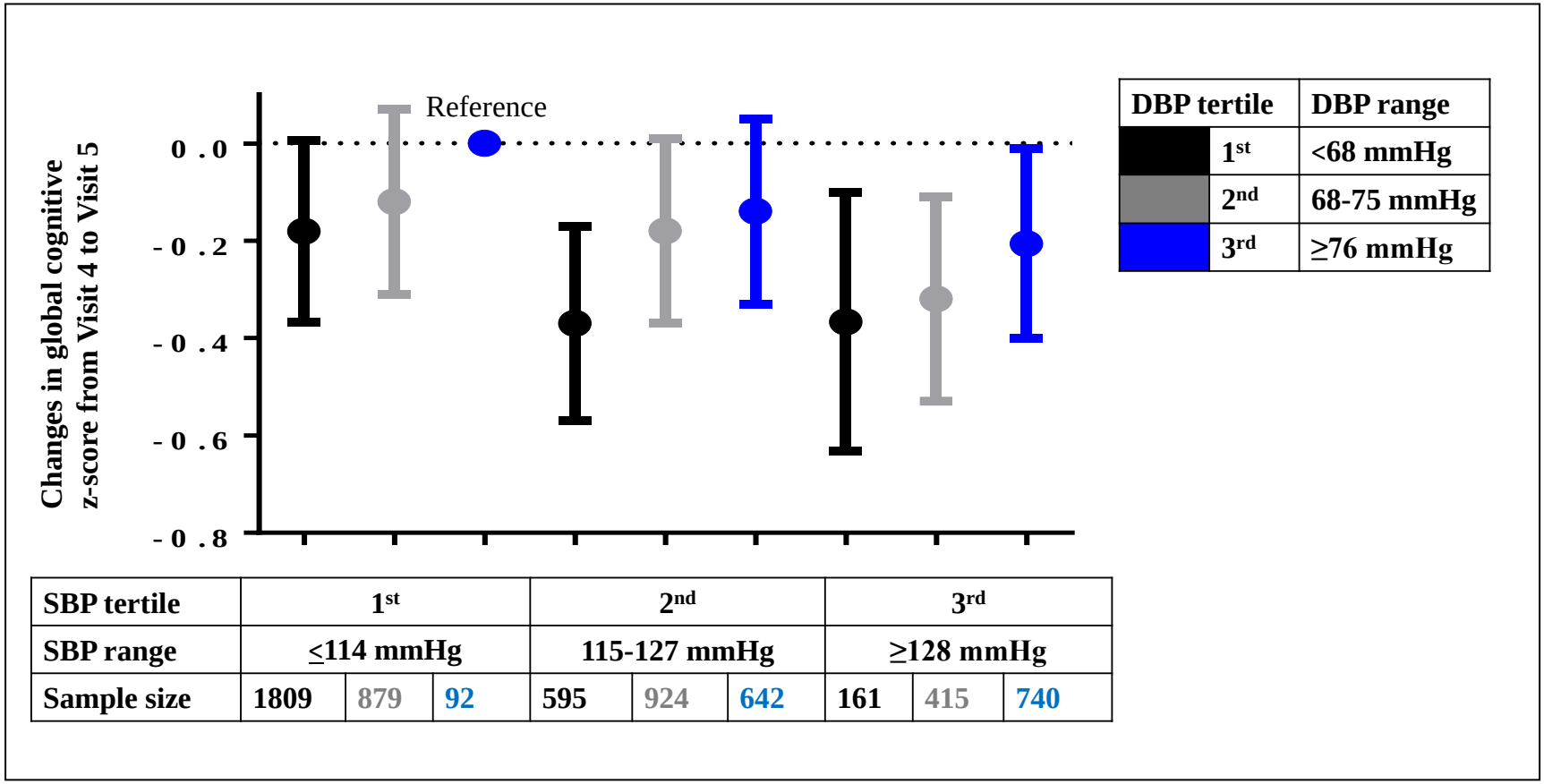
ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. Adjusted βs (95% CIs) associated with 1 SD increases of each BP parameter are shown. 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included: demographic variables (age at baseline, sex, race, education, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (results were shown in models 1 and 2) or mean DBP levels (results were shown in models 3 and 4); ARV_{SBP} (result was shown in model 1) or SD_{SBP} (result was shown in model 2) or ARV_{DBP} (result was shown in model 3) or SD_{DBP} (result was shown in model 4); time interval×mean SBP levels (in models 1 and 2) or time interval×DBP levels (in models 3 and 4); time interval×ARV_{SBP} (in model 1) or time interval×SD_{SBP} (in model 2) or time interval×ARV_{DBP} (in model 3) or time interval×SD_{DBP} (in model 4). Statistical significance was defined as $p<0.05$.

Table S20. Associations between long-term BP levels or variability from Visit 1 to Visit 4 and cognitive change from Visit 4 to Visit 5 according to ApoE ε4 alleles

	ApoE ε4 alleles (0), n=7,637		**ApoE ε4 alleles (≥1), n=3,771**	
	Global *z* score		**Global *z* score**	
Variables	**β (95% CIs)**	**p-value**	**β (95% CIs)**	**p-value**
Model 1:				
Mean SBP*	**-0.05 (-0.07 to -0.02)**	<0.001	-0.02 (-0.07 to 0.02)	0.32
ARV_{SBP}*	0.01 (-0.02 to 0.04)	0.47	-0.01 (-0.05 to 0.03)	0.67
Model 2:				
Mean SBP*	**-0.05 (-0.08 to -0.02)**	<0.001	-0.03 (-0.07 to 0.02)	0.22
SD_{SBP}*	0.02 (-0.01 to 0.04)	0.23	-0.001 (-0.05 to 0.05)	0.95
Model 3:				
Mean DBP*	**0.03 (0.004 to 0.05)**	0.02	**0.08 (0.04 to 0.12)**	<0.001
ARV_{DBP}*	-0.003 (-0.03 to 0.02)	0.82	**-0.07 (-0.11 to -0.03)**	<0.01
Model 4:				
Mean DBP*	**0.03 (0.004 to 0.05)**	0.02	**0.08 (0.04 to 0.12)**	<0.001
SD_{DBP}*	0.001 (-0.02 to 0.02)	0.96	**-0.07 (-0.12 to -0.03)**	<0.01

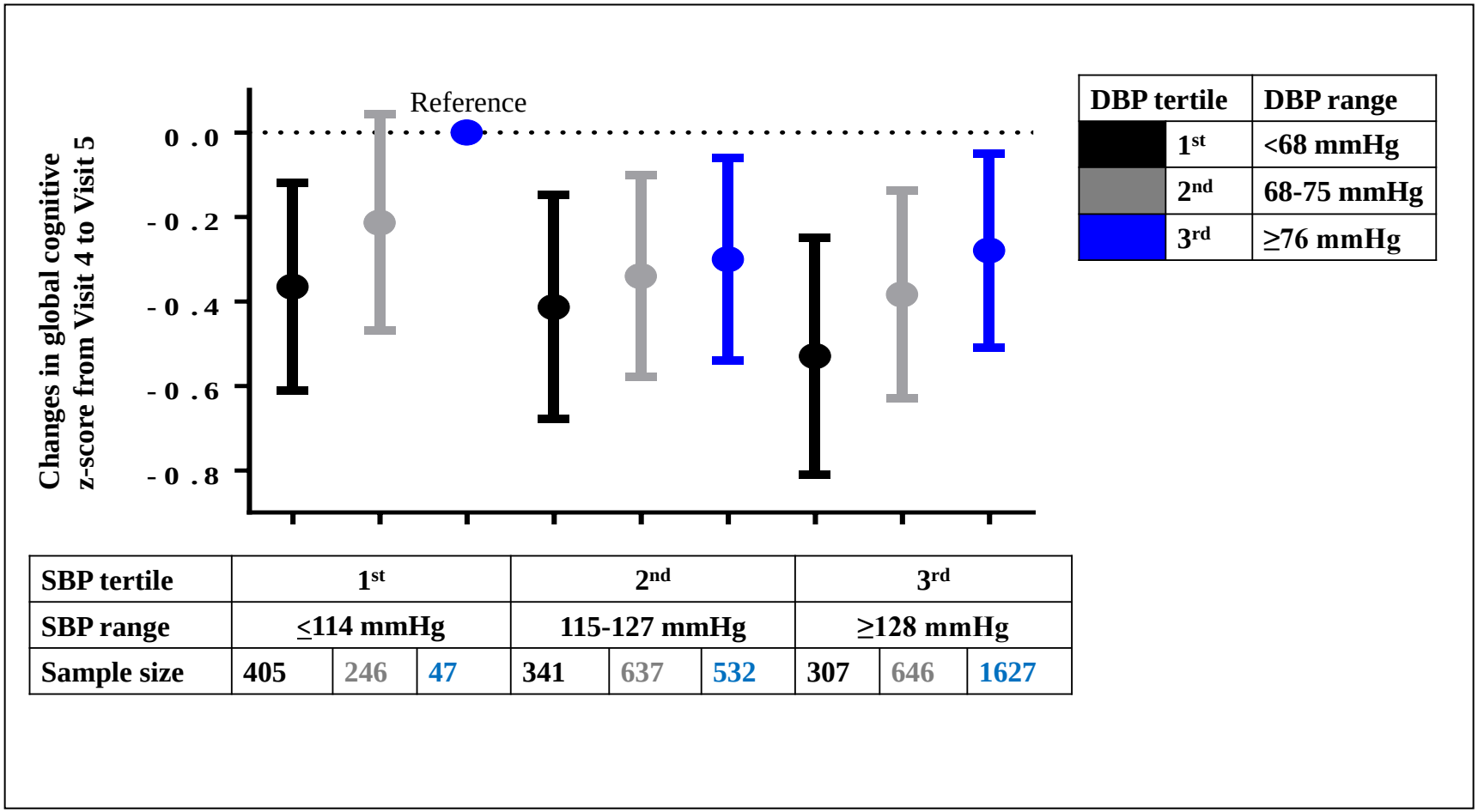
ARV, SD, and mean BP were calculated based upon Visit 1, 2, 3, and 4 BPs. β means standardized regression coefficient. We included interaction terms for each BP parameter (marked with asterisks) and time interval (from Visit 4 to Visit 5; i.e., 15 years) in associations with cognitive change from Visit 4 to Visit 5. Adjusted βs (95% CIs) therefore represent cognitive change associated with a 1-SD increase of each BP parameter over 15 years of follow-up (from Visit 4 to Visit 5). 1 SD increases of each BP parameter are as follows: ARV_{SBP}, per 6.8 mm Hg; ARV_{DBP}, per 3.8 mm Hg; SD_{SBP}, per 5.9 mm Hg; SD_{DBP}, per 3.2 mm Hg; mean SBP, per 15.4 mm Hg; and mean DBP, per 8.6 mm Hg. Models included: demographic variables (age at baseline, sex, race, education, and study center); clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, use of antihypertensive drugs, and prevalent stroke); time interval (from Visit 4 to Visit 5; i.e., 15 years); mean SBP (models 1 and 2) or mean DBP levels (models 3 and 4); ARV_{SBP} (model 1) or SD_{SBP} (model 2) or ARV_{DBP} (model 3) or SD_{DBP} (model 4); time interval×mean SBP levels (results were shown in models 1 and 2) or time interval×DBP levels (results were shown in models 3 and 4); time interval×ARV_{SBP} (result was shown in model 1) or time interval×SD_{SBP} (result was shown in model 2) or time interval×ARV_{DBP} (result was shown in model 3) or time interval×SD_{DBP} (result was shown in model 4). Statistical significance was defined as $p<0.05$.

Figure S1. Antihypertensive medication use (-).



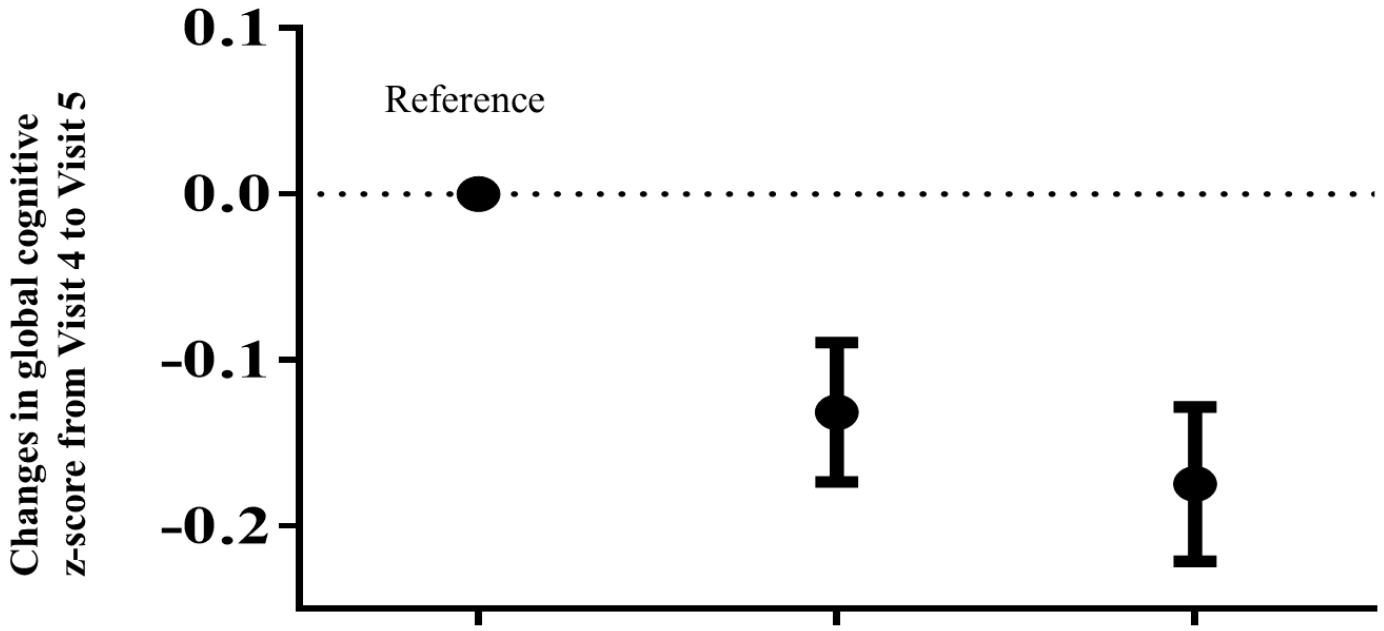
SBP tertile	1st			2nd			3rd		
SBP range	≤114 mmHg			115-127 mmHg			≥128 mmHg		
Sample size	1809	879	92	595	924	642	161	415	740

Figure S2. Antihypertensive medication use (+).



SBP tertile	1st			2nd			3rd		
SBP range	≤114 mmHg			115-127 mmHg			≥128 mmHg		
Sample size	405	246	47	341	637	532	307	646	1627

Figure S3. Associations between mean PP levels and cognitive decline.



PP tertile	1st	2nd	3rd
PP range	≤43 mmHg	44-52 mmHg	≥53 mmHg
Sample size	3558	3706	4144

Supplemental Figure Legends:

Figure S1 and S2. Associations between mean SBP or DBP levels and cognitive decline by the presence or absence of antihypertensive medication use at Visit 4. Participants were stratified into 9 groups using a 3x3 matrix of the tertiles of mean SBP and DBP levels from Visit 1 to Visit 4. Change in global cognitive z scores over 15 years (from Visit 4 to Visit 5) associated with each group are shown. The reference group was defined as participants who were classified into the 1st tertile of SBP and 3rd tertile of DBP. Bars represent adjusted β (95% CIs) of the interaction term between each group and time interval (from Visit 4 to Visit 5; i.e., 15 years). Adjustment factors included demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center) + clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, and prevalent stroke) + time interval + each group.

Figure S3. Associations between mean PP levels and cognitive decline. Participants were stratified into 3 groups using the tertiles of mean PP levels from Visit 1 to Visit 4. Change in global cognitive z scores over 15 years (from Visit 4 to Visit 5) associated with each group are shown. The reference group was defined as participants who were

classified into the 1st tertile of PP. Bars represent adjusted β (95% CIs) of the interaction term between each group and time interval (from Visit 4 to Visit 5; i.e., 15 years). Adjustment factors included demographic variables (age at baseline, sex, race, education, APOE ε4 alleles, and study center) + clinical characteristics at Visit 4 (BMI, smoking, alcohol, total cholesterol, HDL, diabetes, and prevalent stroke) + time interval + each group.