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RESEARCH ARTICLE

Visit-to-visit blood pressure variability and cognitive decline in the oldest-old

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Abstract

INTRODUCTION: The oldest-old (≥90 years) have a high burden of cognitive impairment, yet the role of blood pressure (BP) variability remains unclear. We examined whether visit-to-visit resting systolic BP variability (rSBPV) is associated with cognitive decline.

METHODS: We analyzed *The 90+ Study* participants ($n = 647$) without dementia at baseline who had ≥3 longitudinal BP and cognitive assessments. rSBPV was defined as the root mean square error from within-participant regression of systolic BP on age and categorized as low, medium, or high. Multi-state models estimated transitions between normal cognition, cognitive impairment, and dementia.

RESULTS: Compared with medium rSBPV, high rSBPV was associated with higher hazards of transitioning from normal cognition to cognitive impairment (hazard ratio [HR] 1.36, 95% confidence interval [CI] 1.05–1.74), from normal cognition to dementia (HR 2.90, 95% CI 1.26–6.69), and from cognitive impairment to dementia (HR 1.44, 95% CI 1.06–1.96).

DISCUSSION: Higher rSBPV is associated with greater cognitive decline in older adults.

KEYWORDS
aging, blood pressure variability, cardiovascular, cognitive decline, cognitive impairment, dementia, longitudinal cohort, multi-state modeling, oldest-old, The 90+ Study

HIGHLIGHTS

- Higher long-term systolic blood pressure variability (BPV) was associated with cognitive decline in the oldest-old
- Intermediate and lower systolic BPV were not associated with worse cognitive outcomes
- Cognitive trajectories are often non-linear; ≈30% of transitions were from cognitively impaired to normal cognition

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RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources. We cited prior publications describing the relationship between long-term blood pressure variability (BPV) and cognitive outcomes in adult populations.
2. **Interpretation**: Our findings extend the association between greater visit-to-visit resting systolic BPV and cognitive decline to adults aged 90 years and older, a population underrepresented in clinical research. Compared with intermediate resting systolic BPV, high resting systolic BPV was associated with greater hazards of cognitive impairment and dementia, whereas low resting systolic BPV was not significantly associated with worse cognitive outcomes.
3. **Future directions**: Future work should clarify the mechanisms linking long-term BPV to cognitive decline in the oldest-old, including the potential contributions of arterial stiffness and impaired cerebral autoregulation, frailty, and neurodegenerative disease. Prospective studies are needed to determine to what extent long-term BPV can be modified in late life and whether therapies targeting BPV can improve cognitive outcomes.

1 | INTRODUCTION

The "oldest-old" (individuals ≥90 years of age) are the fastest-growing segment of the U.S. population[1] and disproportionately utilize health care resources.[2] Cognitive dysfunction is common in this cohort, with dementia affecting about 40%,[3] and contributes to increased hospitalizations and mortality.[4,5] Systemic hemodynamic states, specifically blood pressure variability (BPV), may represent a modifiable risk factor for the development of cognitive impairment. BPV describes an individual's variation in blood pressure (BP) over time and can be categorized according to intervals between measurements as either acute (i.e., inter-beat intervals), short-term (e.g., within 24 h), or long-term (across days, weeks, or months).[6] Shorter-term BP variations are influenced by various physiological mechanisms, which include arterial compliance, chemical signals, autonomic reflexes, behavioral factors, and circadian patterns.[7] The contributors to long-term BPV are less well understood and likely involve arterial stiffness[8] and adherence to antihypertensive medications.[9,10]

Greater short-term and long-term BPV have been associated with cognitive impairment in large prospective cohorts of older adults.[11–16] Moreover, increased BPV has been linked to chronic cardiovascular and cerebrovascular disease, including atherosclerosis, arteriolosclerosis, and microvascular infarcts, as well as Alzheimer's disease pathology.[16,17] In most longitudinal studies investigating the relationship between BPV and cognitive outcomes, mean participant ages have ranged from 65 to 80 years.[11,17–19] However, to our knowledge, the relationship between BPV and cognitive decline has not been studied specifically in the oldest-old population, which may have distinct biological characteristics and adaptive mechanisms. Notably, prior investigations have demonstrated that associations between dementia risk and cardiovascular risk factors—such as hypertension and diabetes—observed in younger populations do not generalize to the oldest-old.[20,21] In fact, the onset of hypertension at age 80 years and older has been associated with a *reduced* risk of dementia,[20] suggesting that this age group may possess unique physiological adaptations conferring resilience.

In this prospective cohort study of adults 90 years of age and older, we examined the association between visit-to-visit resting systolic BPV (rSBPV) and cognitive decline. This relationship is clinically relevant given the potential for BPV to serve as both a predictive biomarker and a modifiable risk factor for cognitive impairment. Based on prior studies in middle-aged and older adult populations,[11,17,18] we hypothesized that greater visit-to-visit rSBPV would be associated with cognitive decline.

2 | METHODS

2.1 | Participants and eligibility criteria

Participants were drawn from *The 90+ Study*, a community-based longitudinal cohort of adults ≥90 years of age that began in 2003. The original cohort consisted of surviving participants from The Leisure World Cohort Study (LWCS), an epidemiological study in a retirement community in Orange County, California (USA), that was established in the early 1980s.[22] Starting in 2014, the study expanded to include volunteers 90 years of age and older through a variety of recruitment strategies beyond the LWCS. Although participants from the LWCS were recruited regardless of cognitive status, non-cohort volunteers were eligible if they had no dementia or only mild dementia.[23] Participants underwent comprehensive assessments every 6 months, including standardized BP measurements, neurological and neuropsychological evaluations, and assessments of medical history, family history, and daily functioning. To reduce missing data, visits took place at the research facility or in participants' homes, using relatively brief assessments designed to accommodate sensory and motor limitations.[24] We included participants with concurrent BP and cognitive assessments at three or more visits. Participants were excluded if they had a clinical diagnosis of dementia at baseline, as determined by the evaluating clinician.

2.2 | Consent statement

All participants or their designated informants provided written informed consent under protocols approved by the University of California Irvine Institutional Review Board.

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2.3 | Blood pressure measurements and cognitive evaluations

BP measurements were obtained at each visit as part of vital sign checks. BP was measured with the participant seated at rest in a quiet room at the completion of the initial interview. The duration of rest before measurement was not specified in the study protocol. A single BP measurement was obtained; multiple measurements were not obtained and averaged. According to the standardized protocol, the cuff was placed on the left arm, and BP was measured over the brachial artery; the right arm could be used when BP measurement from the left arm was contraindicated (e.g., following mastectomy).

Baseline cognitive status was determined by clinical evaluation, with follow-up assessments conducted at 6-month intervals. At each visit, clinicians classified participants as having normal cognition, cognitive impairment (not meeting criteria for dementia), or dementia based on clinical examination and interview findings. Trained staff administered the Clinical Dementia Rating Sum of Boxes (CDR-SB; range: 0–18; higher scores indicate greater impairment),[25] the Modified Mini-Mental State Examination (3MS; range: 0–100; higher scores indicate better cognitive performance),[26] and the Mini-Mental State Examination (MMSE; range: 0–30; higher scores indicate better cognitive performance).[27]

2.4 | Blood pressure variability and cognitive outcomes

The primary exposure was within-individual visit-to-visit rSBPV, calculated as the root mean square error (RMSE) from a participant-specific linear regression of systolic BP on age. RMSE was selected because it quantifies fluctuations around each participant's estimated longitudinal BP trajectory, thereby distinguishing visit-to-visit variability from systematic changes in systolic BP associated with advancing age. This approach is consistent with prior longitudinal research using participant-specific regression residuals to quantify visit-to-visit BPV.[17] In contrast, other measures, such as the standard deviation (SD) and coefficient of variation (COV), may incorporate both sources of variation because they quantify dispersion around the participant's overall mean BP. rSBPV was calculated using all available BP measurements collected during follow-up and was treated as a time-invariant participant-level exposure. A fixed baseline-window approach was not used because the limited number of BP measurements within an early window would have yielded unstable participant-level variability estimates and substantially reduced the eligible sample. Participants were categorized into low (<1st quartile), medium (≥1st quartile and ≤3rd quartile), and high (>3rd quartile) rSBPV groups based on the sample distribution of calculated rSBPV values. In the primary analyses, rSBPV was categorized to allow comparisons across low, medium, and high groups without assuming a linear exposure–hazard relationship. We focused on systolic BPV, as prior studies have demonstrated stronger associations with cognitive outcomes compared with diastolic BPV.[11,28] The primary cognitive outcome was cognitive-status transition (i.e., normal cognition to cognitive impairment, normal to dementia, cognitive impairment to dementia, or cognitive impairment to normal cognition) across study visits. Secondary cognitive outcomes were longitudinal changes in CDR-SB, 3MS, and MMSE scores.

2.5 | Statistical analysis

Participants entered the analysis at the baseline visit and were followed until dementia diagnosis, death, or end of follow-up, whichever occurred first. Using age as the time scale, we estimated age-specific state occupation probabilities for each cognitive state by rSBPV group using a multi-state model with the Aalen–Johansen estimator.[29] The primary analysis used a semi-progressive transition structure that allowed transitions from normal cognition to cognitive impairment, normal cognition to dementia, cognitive impairment to dementia, and cognitive impairment to normal cognition, while treating dementia as an absorbing state. Transitions from dementia back to normal cognition were not modeled due to their rarity, since only nine such transitions were observed. Based on the estimated state-occupation probabilities, we also derived the expected time spent in each cognitive state by integrating the estimated probabilities over the age range of 90 to 105 years, because observations beyond age 105 years were sparse and the resulting estimates were less stable.

In addition, we fitted multi-state Cox proportional hazards models to estimate transition-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for differences in transition hazards across rSBPV groups (with the medium rSBPV group as the reference). The primary Cox analysis used the same semi-progressive transition structure as the Aalen–Johansen analysis. Each possible transition type was treated as a separate risk set using a start–stop (entry age, exit age) formulation, with baseline hazards stratified by transition. We evaluated both a shared-effect specification, which constrained the rSBPV group association to be common across transitions, and a transition-specific specification, which allowed the rSBPV group association to vary by transition.

Models were adjusted for sex, race, education, use of medications potentially affecting BP, baseline systolic BP, baseline comorbidities (hypertension, stroke, transient ischemic attack, diabetes, and heart disease), and baseline cognitive status. For transitions representing cognitive worsening (normal cognition→cognitive impairment, normal cognition→dementia, cognitive impairment→dementia), HR >1 indicates a higher hazard of worsening; for the recovery transition (cognitive impairment→normal cognition), HR >1 indicates a higher hazard of reversion to normal cognition. As a sensitivity analysis, we fitted a fully bidirectional multi-state Cox model allowing all observed transitions among cognitive states, including transitions out of dementia.

To evaluate the robustness of our findings to the choice of BPV measure, secondary analyses examined alternative measures of visit-to-visit BPV calculated from the same participant-level BP observations used to calculate RMSE, including the within-participant SD, COV (100 × SD/mean SBP), and variation independent of the mean (VIM). VIM was calculated as SD × (M/mean SBP)$^{\hat{}}\beta$, where M denotes the mean of

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participant-specific mean SBP values and β was estimated by nonlinear power regression of SD on mean SBP across participants. Participants were categorized into low (<1st quartile), medium (≥1st quartile and ≤3rd quartile), and high (>3rd quartile) groups using the distribution of each measure. Shared-effect and transition-specific multi-state Cox models were refitted under both semi-progressive and bidirectional frameworks, using age as the time scale, the same pre-specified covariates, and the medium group as the reference.

Secondary analyses used linear mixed-effects models to examine associations between rSBPV (modeled continuously) and longitudinal CDR-SB, 3MS, and MMSE scores. To determine the functional forms of follow-up visit number and rSBPV, we compared models including linear, quadratic, and cubic terms for visit number and linear or quadratic terms for rSBPV. Model selection was guided by the Akaike information criterion (AIC), balancing model fit with parsimony. The selected models included cubic terms for visit number, with linear or quadratic terms for rSBPV depending on the cognitive outcome. Models included participant-specific random effects to account for repeated measures and adjusted for baseline age, sex, race, education, use of medications potentially affecting BP, baseline mean BP, and baseline comorbidities. Each model was additionally adjusted for baseline cognitive status and the baseline value of the corresponding cognitive measure. As a visual summary of the model results, we used the fitted models to estimate visit-specific predicted means at two representative rSBPV levels defined as the median ± interquartile range (IQR)/2 (High = median + IQR/2; Low = median − IQR/2), holding other covariates at their reference levels or sample means. We then calculated the visit-specific contrast as the difference in predicted means (High − Low) and plotted this contrast with pointwise 95% CIs. Analyses above were conducted in R using the survival, mstate, and nlme packages.

3 | RESULTS

The data query conducted on November 7, 2023, identified 1358 unique participants. Among these, 470 were excluded due to having fewer than three visits with BP data, 236 were excluded for having a diagnosis of dementia at baseline, and 5 were excluded due to having fewer than three visits with cognitive data (Figure 1). The final sample consisted of 647 participants (Table 1). Participants contributed a mean of 7.9 BP measurements (SD = 4.4; median = 7, IQR = 5–10; range = 3–26) to the rSBPV calculation, and 88 participants (13.6%) contributed exactly 3 BP measurements. Mean rSBPV was 14.11 mmHg (SD = 6.77), with a median of 13.09 mmHg (IQR = 9.84–17.55) and a range of 0.00–49.24 mmHg; the rSBPV ranges were <9.85 mmHg for the low group, ≥9.85 to ≤17.55 mmHg for the medium group, and >17.55 mmHg for the high group. Corresponding descriptive values for resting diastolic blood pressure variability (rDBPV) were a mean of 7.81 mmHg (SD = 3.68), a median of 7.55 mmHg (IQR = 5.61–9.71), and a range of 0.00–32.66 mmHg; the rDBPV ranges were <5.61 mmHg for the low group, ≥5.61 to ≤9.71 mmHg for the medium group, and >9.71 mmHg for the high group. Of the 647 participants included in the final sample, 408 (63.1%)

TABLE 1 Clinical characteristics of participants included ($n = 647$).

Age at baseline visit, years	**92.6 (2.3)**
Sex, female, *n* (%)	408 (63.1%)
Race/ethnicity, *n* (%)	
White	626 (96.8%)
Black	1 (0.2%)
Asian/Pacific Islander	14 (2.2%)
Spanish/Hispanic/Latino	6 (0.9%)
Education, *n* (%)	
Did not complete 8th grade	5 (0.8%)
Some high school	20 (3.1%)
High school graduate	111 (17.2%)
Vocational school	30 (4.6%)
Some college	165 (25.5%)
College graduate	133 (20.6%)
Some graduate school	44 (6.8%)
Advanced degree	139 (21.4%)
Baseline sitting systolic BP, mmHg	141.3 (20.4)
Baseline sitting diastolic BP, mmHg	72.5 (10.9)
Baseline cognitive status, *n* (%)	
Normal	384 (59.4%)
Cognitive impairment (no dementia)	263 (40.6%)
Cognitive status at last visit, *n* (%)	
Normal	209 (32.2%)
Cognitive impairment	189 (29.2%)
Dementia	249 (38.5%)
Baseline 3MS total score	90.3 (8.3)
Baseline MMSE total score	26.8 (2.6)
Baseline CDR-SB score	0.4 (0.7)
Number of visits	8.2 (4.5)
Follow-up duration, years	4.4 (2.6)
Clinical comorbidities at baseline, *n* (%)	
History of hypertension	354 (54.7%), *n* = 12 missing
History of stroke	39 (6.0%), *n* = 2 missing
History of TIA	99 (15.3%), *n* = 9 missing
History of diabetes mellitus	66 (10.2%), *n* = 1 missing
History of heart disease	308 (47.6%)
Medications at baseline that may affect	
Blood pressure *n* (%)	460 (71.1%), *n* = 14 missing
rSBPV, mmHg	14.11 (6.77)
Low rSBPV group range, mmHg	< 9.85
Medium rSBPV range, mmHg	9.85–17.55
High rSBPV range, mmHg	> 17.55
rDBPV, mmHg	7.81 (3.68)
Low rSBPV group range, mmHg	≤5.61
Medium rSBPV range, mmHg	> 5.61 to < 9.71
High rSBPV range, mmHg	≥9.71

Note: Continuous variables are shown as mean (SD) unless otherwise specified.

Abbreviations: 3MS, Modified Mini-Mental State Examination; BP, blood pressure; CDR-SB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini-Mental State Examination; rDBPV, resting diastolic blood pressure variability; rSBPV, resting diastolic blood pressure variability; TIA, transient ischemic attack.

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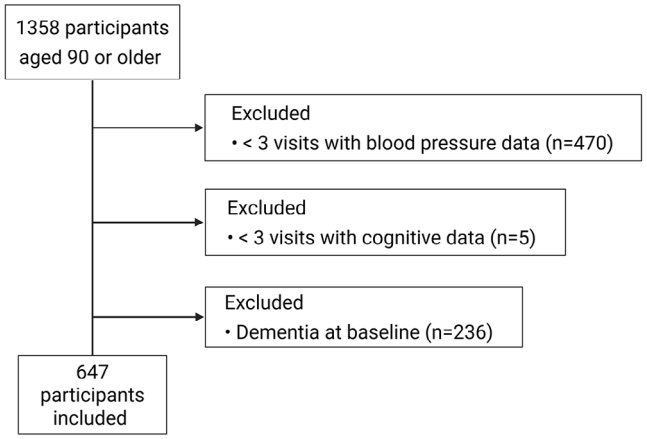


FIGURE 1 Flow diagram of participants included.

were female. The mean age at the first visit was 92.6 years (SD = 2.3). At baseline, 384 participants (59.4%) had normal cognition and 263 (40.6%) had cognitive impairment. Over a mean follow-up duration of 4.4 years (SD = 2.6), participants completed a mean of 8.2 visits (SD = 4.5). By the final visit, 116 participants transitioned from baseline normal cognition to cognitive impairment, and 249 transitioned from either baseline normal cognition or cognitive impairment to dementia. Separately, across all consecutive visit-to-visit transition events observed during follow-up, 373 events (29.8% of all transition events) were reversions from cognitive impairment to normal cognition. These events occurred in 284 unique participants. Among these participants, 215 later transitioned to either cognitive impairment or dementia after their first cognitive impairment-to-normal cognition transition; at the final observed visit, 95 had normal cognition, 90 had cognitive impairment, and 99 had dementia.

3.1 | Primary outcomes

3.1.1 | Aalen–Johansen estimators

Aalen–Johansen estimates are presented in eTable 1. Under the semi-progressive multi-state framework, the high rSBPV group had the longest expected time (ET) in dementia (ET = 7.77 years, 95% CI 6.87–8.55), followed by the low rSBPV group (ET = 7.30 years, 95% CI 6.45–8.17). In contrast, the medium rSBPV group had the shortest expected time in dementia (ET = 6.15 years, 95% CI 5.53–6.76) and the longest expected time with normal cognition (ET = 5.81 years, 95% CI 5.14–6.51), compared with the low (ET = 4.85 years, 95% CI 3.99–5.70) and high rSBPV groups (ET = 4.41 years, 95% CI 3.69–5.34).

Figure 2 shows the Aalen–Johansen estimates of age-specific state-occupation probabilities for normal cognition, cognitive impairment, and dementia by rSBPV group under the semi-progressive specification. Across ages 90–105 years, the probability of retaining normal cognition decreased steadily in all three rSBPV groups, accompanied by a steady increase in the probability of being in the dementia category.

3.1.2 | Cox proportional hazards model

In transition-specific multi-state Cox models adjusting for pre-specified covariates (Figure 3), high rSBPV (vs medium) was associated with higher hazards of cognitive worsening, including transitions from cognitive impairment to dementia (HR 1.44, 95% CI 1.06–1.96), normal cognition to dementia (HR 2.90, 95% CI 1.26–6.69), and normal cognition to cognitive impairment (HR 1.36, 95% CI 1.05–1.74). High rSBPV was not significantly associated with reversion from cognitive impairment to normal cognition (HR 1.03, 95% CI 0.79–1.35). Low rSBPV (vs medium) was not significantly associated with any transition, including transitions from cognitive impairment to dementia (HR 1.18, 95% CI 0.87–1.60), normal cognition to dementia (HR 1.19, 95% CI 0.50–2.87), normal cognition to cognitive impairment (HR 1.06, 95% CI 0.82–1.37), and cognitive impairment to normal cognition (HR 1.15, 95% CI 0.87–1.52). In the shared-effect Cox model, which constrained the rSBPV association to be common across transitions, high rSBPV (vs medium) was associated with a higher overall rate of cognitive-state transitions (HR 1.30, 95% CI 1.11–1.52), whereas low rSBPV (vs medium) showed no evidence of significant association (HR 1.12, 95% CI 0.95–1.32).

Because the number of individuals at risk varies over follow-up in the multi-state counting-process framework, visit-specific at-risk counts are presented in eTables 2 and 3.

3.2 | Secondary outcomes

In longitudinal mixed-effects models with polynomial terms for follow-up visits (eFigures 1–3), the High–Low rSBPV contrast was near 0 at early visits for all three outcomes, suggesting minimal differences in predicted cognitive performance early in follow-up. With longer follow-up, higher rSBPV was associated with higher predicted CDR-SB scores and lower predicted 3MS and MMSE scores, consistent with progressively worse cognitive trajectories. Pointwise 95% CIs for the High–Low contrast first excluded 0 at approximately visit 22.0 for CDR-SB, 14.5 for 3MS, and 17.1 for MMSE (Figure 4). The magnitude of the contrast generally increased thereafter. CIs widened at later visits because fewer observations were available at longer follow-up durations. The number of observations contributing to each visit-specific longitudinal cognitive trajectory estimate by outcome is summarized in eTable 4.

Baseline cognitive performance was strongly associated with subsequent longitudinal cognitive scores. Higher baseline CDR-SB scores were associated with higher longitudinal CDR-SB scores (0.85 [95% CI 0.73–0.98] per 1-point higher baseline CDR-SB), whereas higher baseline 3MS and MMSE scores were associated with higher longitudinal 3MS (0.80 [95% CI 0.75–0.85]) and MMSE scores (0.70 [95% CI 0.65–0.75]), respectively. Baseline cognitive impairment was associated with lower longitudinal 3MS and MMSE scores, whereas its association with longitudinal CDR-SB was not statistically significant (CDR-SB: −0.01 [95% CI −0.19 to 0.17]; 3MS: −0.77 [95% CI −1.55 to −0.01]; MMSE: −0.54 [95% CI −0.80 to −0.28]).

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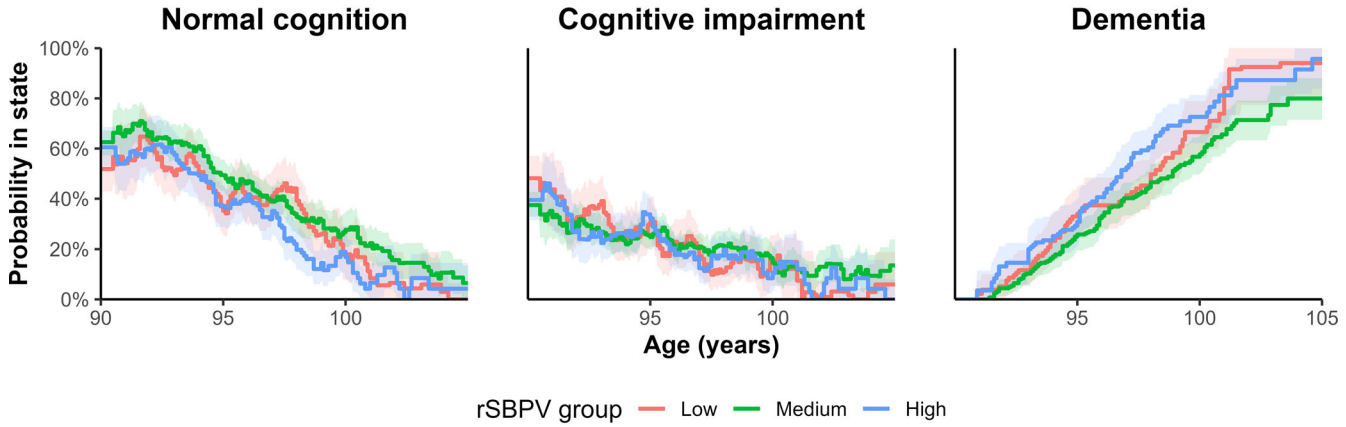


FIGURE 2 Aalen–Johansen curves for cognitive status by visit-to-visit resting systolic blood pressure variability (rSBPV) group within a semi-progressive multi-state framework. The y-axis represents the estimated probability of being in each state at a given age. The x-axis represents age, and separate curves are shown for the low, medium, and high rSBPV groups. The shaded areas represent pointwise 95% confidence intervals using participant-level bootstrap resampling within each rSBPV group. In each bootstrap sample, participants were resampled and all repeated observations and transitions for each selected participant were retained together to preserve within-participant correlation. For better visualization, the figure displays results only for ages 90–105 years, since observations beyond age 105 years were sparse and the resulting curves became less stable.

Effect of rSBPV on Transition Hazards

Transition	Events (group/ref)	Hazard ratio (95% CI)
high rSBPV vs medium rSBPV		
cognitive impairment → dementia	56/95	1.44 (1.06–1.96)
cognitive impairment → normal cognition	85/171	1.03 (0.79–1.35)
normal cognition → dementia	14/17	2.90 (1.26–6.69)
normal cognition → cognitive impairment	126/237	1.36 (1.05–1.74)
shared effect	281/520	1.30 (1.11–1.52)
low rSBPV vs medium rSBPV		
cognitive impairment → dementia	43/95	1.18 (0.87–1.60)
cognitive impairment → normal cognition	81/171	1.15 (0.87–1.52)
normal cognition → dementia	10/17	1.19 (0.50–2.87)
normal cognition → cognitive impairment	97/237	1.06 (0.82–1.37)
shared effect	231/520	1.12 (0.95–1.32)

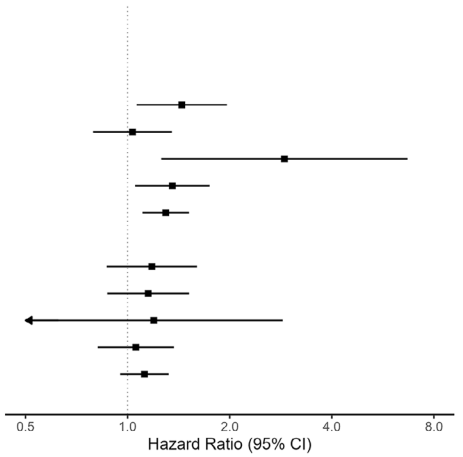


FIGURE 3 Association of visit-to-visit resting systolic blood pressure variability (rSBPV) with cognitive-state transition hazards from multi-state Cox models. Transition-specific Cox models were used to estimate transition-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for cognitive-state transitions comparing high versus medium rSBPV and low versus medium rSBPV. Points indicate HRs, and horizontal lines indicate 95% CIs; the vertical dashed line denotes HR = 1. An HR >1 (< 1) indicates a higher (lower) transition rate relative to the medium rSBPV reference group. The top block shows high versus medium rSBPV, and the bottom block shows low versus medium rSBPV. The "shared effect" rows list results from the Cox model that constrains the rSBPV effect to be the same across transitions while allowing transition-specific baseline hazards.

We performed a supplementary analysis examining rDBPV using an approach analogous to the primary rSBPV analyses (eFigures 4 and 5). Specifically, rDBPV was calculated as the RMSE from a participant-specific linear regression of diastolic BP (DBP) on age. Participants were categorized into low, medium, and high rDBPV groups based on the sample distribution of calculated rDBPV values, using the 25th and 75th percentiles as cut points. The rDBPV findings were less consistent with the primary rSBPV findings. In the semi-progressive framework, high rSBPV versus medium rSBPV was associated with higher hazards of cognitive impairment to dementia (HR 1.44, 95% CI 1.06–1.96), normal cognition to dementia (HR 2.90, 95% CI 1.26–6.69), and normal cognition to cognitive impairment (HR 1.36, 95% CI 1.05–1.74). In contrast, the corresponding high versus medium rDBPV estimates were closer to the null and not statistically significant: cognitive impairment to dementia (HR 0.86, 95% CI 0.63–1.17), normal cognition to dementia (HR 1.11, 95% CI 0.48–2.56), and normal cognition to cognitive

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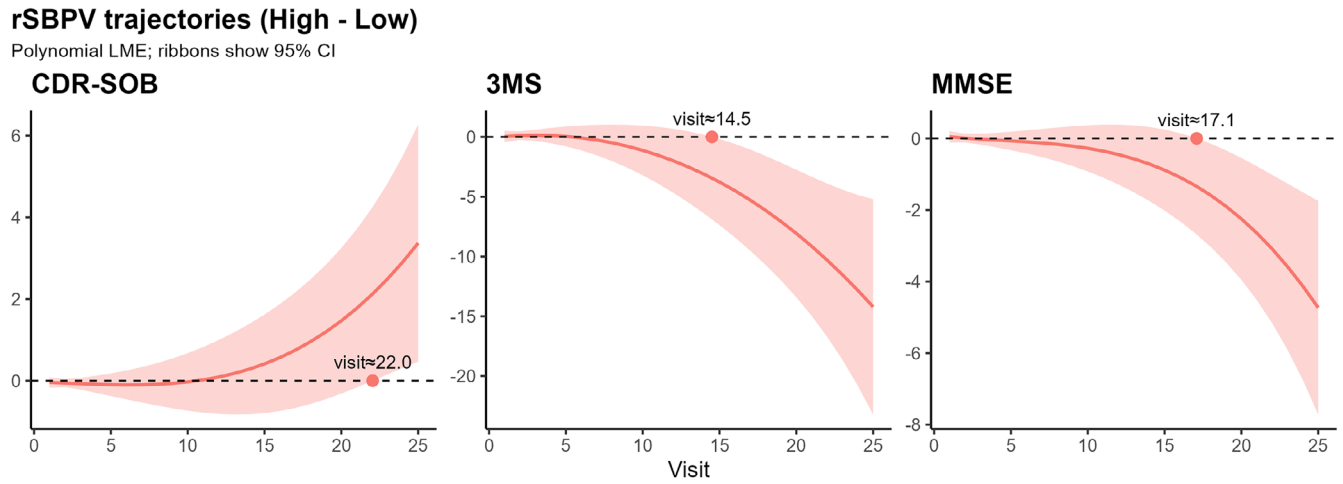


FIGURE 4 Predicted High–Low visit-to-visit resting systolic blood pressure variability (rSBPV) contrasts for secondary cognitive outcomes. Polynomial linear mixed-effects models were used to estimate visit-specific predicted differences (High − Low) for Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Modified Mini-Mental State Examination (3MS), and Mini-Mental State Examination (MMSE). High and low rSBPV levels were defined as the median root mean square error (RMSE) ± interquartile range (IQR)/2, with other covariates fixed at reference values or sample means. Solid lines show estimated mean differences and shaded bands show 95% confidence intervals (CIs); the dashed horizontal line at 0 is included as a visual reference for no difference between the high- and low-rSBPV groups. Labeled points indicate the first visit at which the 95% CI for the contrast excludes 0. Higher CDR-SB scores and lower 3MS and MMSE scores indicate greater impairment.

impairment (HR 1.22, 95% CI 0.95–1.56). The shared-effect estimate also differed between rSBPV and rDBPV analyses (rSBPV: HR 1.30, 95% CI 1.11–1.52; rDBPV: HR 1.00, 95% CI 0.85–1.18).

3.3 | Sensitivity analyses

In the bidirectional transition model, Aalen–Johansen–based expected time estimates and multi-state Cox results were consistent with the primary semi-progressive analysis (eTable 5; eFigures 6 and 7). Secondary-outcome mixed-effects results were also similar under an alternative definition of high and low rSBPV (mean ± SD in place of median ± IQR/2; eFigure 8).

We also repeated the primary analyses after excluding participants with exactly three BP measurements. The results were generally consistent with those of the primary analysis. In the primary semi-progressive analysis, high versus medium rSBPV was associated with cognitive impairment→dementia (HR 1.44, 95% CI 1.06 to 1.96), normal cognition→dementia (HR 2.90, 95% CI 1.26 to 6.69), and normal cognition→cognitive impairment (HR 1.36, 95% CI 1.05 to 1.74), but not cognitive impairment→normal cognition (HR 1.03, 95% CI 0.79 to 1.35). After excluding participants with exactly three BP measurements, the corresponding estimates remained similar, and the pattern of statistical significance was unchanged: HR 1.44 (95% CI 1.05–1.98), HR 2.42 (95% CI 1.04 to 5.64), HR 1.35 (95% CI 1.05 to 1.76), and HR 1.05 (95% CI 0.79 to 1.38), respectively. The shared-effect estimate also remained significant and nearly unchanged (primary analysis: HR 1.30, 95% CI 1.11 to 1.52; sensitivity analysis: HR 1.31, 95% CI 1.11 to 1.54) (eFigures 9 and 10). Associations comparing low versus medium rSBPV remained non-significant in both analyses.

In semi-progressive shared-effect models, high rSBPV (vs medium), defined separately using each alternative metric, was associated with higher transition hazards when quantified using SD (HR 1.18, 95% CI 1.01–1.38), COV (HR 1.24, 95% CI 1.07–1.44), and VIM (HR 1.25, 95% CI 1.07–1.45). Transition-specific estimates for cognitive worsening were generally closer to the null than the corresponding RMSE-based estimates, and statistical significance varied across measures. For transitions from normal cognition to dementia, the HRs were 2.18 (95% CI 0.90–5.33) using SD, 2.47 (95% CI 1.10–5.53) using COV, and 2.32 (95% CI 1.03–5.20) using VIM, with statistically significant associations for COV and VIM. For transitions from cognitive impairment to dementia, the corresponding HRs were 1.08 (95% CI 0.78–1.51), 1.23 (95% CI 0.91–1.68), and 1.37 (95% CI 1.01–1.85), respectively, with a statistically significant association only for VIM. Associations with transitions from normal cognition to cognitive impairment were nonsignificant for all three measures: SD (HR 1.11, 95% CI 0.85–1.44), COV (HR 1.13, 95% CI 0.87–1.46), and VIM (HR 1.06, 95% CI 0.81–1.38). Low rSBPV (vs medium) was associated with a higher hazard of reversion from cognitive impairment to normal cognition when quantified using COV (HR 1.35, 95% CI 1.03–1.77) and VIM (HR 1.35, 95% CI 1.03–1.76), whereas the corresponding association when quantified using SD was nonsignificant (HR 1.27, 95% CI 0.96–1.68) (eFigures 11–13).

In bidirectional shared-effect models, high rSBPV (vs medium) remained associated with higher transition hazards when quantified using COV (HR 1.23, 95% CI 1.06–1.42) and VIM (HR 1.26, 95% CI 1.09–1.46), whereas the association when quantified using SD was nonsignificant (HR 1.16, 95% CI 0.99–1.36). In transition-specific bidirectional models, low rSBPV (vs medium) was associated with a higher hazard of reversion from cognitive impairment to normal cognition regardless of the measure used: SD (HR 1.33, 95% CI 1.01–1.75), COV

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(HR 1.42, 95% CI 1.09–1.86), and VIM (HR 1.38, 95% CI 1.06–1.80) (eFigures 14–16).

4 | DISCUSSION

In this prospective analysis of individuals 90 years of age and older who were dementia-free at baseline, higher visit-to-visit rSBPV (vs medium rSBPV) was associated with longitudinal cognitive trajectories, including higher hazards of progression from normal cognition to cognitive impairment and dementia, and from cognitive impairment to dementia. In contrast, low rSBPV (vs medium rSBPV) showed no clear evidence of association with cognitive state transitions in the primary RSME-based analysis. Secondary longitudinal analyses of CDR-SB, 3MS, and MMSE scores indicated that baseline cognitive performance strongly predicted subsequent trajectories. Higher rSBPV was also associated with increasingly worse model-predicted cognitive trajectories over time, with minimal separation early in follow-up and progressively larger differences later in follow-up. These results align with prior findings demonstrating stronger associations between BPV and dementia risk with advancing age.[18,30]

Sensitivity analyses using alternative rSBPV metrics (SD, COV, and VIM) generally supported the primary RMSE-based findings, with higher rSBPV associated with increased overall cognitive-state transition hazards across all three measures in the semi-progressive models. However, associations with individual transitions were generally attenuated and less consistent than those observed using RMSE, particularly for progression from normal cognition to cognitive impairment and from cognitive impairment to dementia. Notably, lower rSBPV measured using COV and VIM was associated with a higher hazard of reversion from cognitive impairment to normal cognition, an association not observed with RMSE. These findings suggest that the overall relationship between rSBPV and cognitive-state transitions is relatively robust across BPV metrics, although associations with specific cognitive transitions may depend on how BPV is quantified.

In secondary analyses, associations for rDBPV were less consistent than those observed for rSBPV. The categorical rSBPV and rDBPV groups showed only partial overlap; for example, among participants classified as having high rSBPV, only 43.8% were also classified as having high rDBPV. These results suggest that systolic and diastolic BPV may capture related but distinct aspects of BP regulation in the oldest-old. One possible explanation for the stronger associations observed with rSBPV is that, in older adults, systolic variability more closely reflects large-artery stiffness and impaired buffering of pulsatile pressure,[31] which may affect cognition through multiple mechanisms including endothelial dysfunction, blood–brain barrier breakdown, and impaired autoregulation. With advancing age, SBP generally continues to rise, whereas DBP tends to plateau and then decline after ≈50–60 years of age,[32,33] leading to widening pulse pressure. Because DBP is influenced by the competing effects of peripheral vascular resistance, arterial compliance, cardiac output, and treatment-related factors, greater rDBPV may arise from several distinct hemodynamic patterns rather than represent a single vascular phenotype,[34] which could reduce its specificity as a marker of cerebrovascular injury and reduce the strength of cognitive associations. This interpretation remains speculative, however. Prior studies have associated both systolic and diastolic BPV with worse cognitive outcomes,[12,17] whereas some studies have found longitudinal or domain-specific associations that were limited primarily to SBPV.[35–37] Therefore, our findings suggest that rSBPV may be a more sensitive marker of cognitive risk in this oldest-old cohort but do not establish that the causal or mechanistic contributions for rSBPV differ from those of rDBPV.

Our findings extend prior evidence linking greater BPV with worse cognitive outcomes in middle-aged and older adults to the oldest-old, a population underrepresented in BPV research. Higher BPV has been linked to other adverse neurological outcomes, including stroke, small-vessel cerebrovascular disease,[38–40] as well as blood-based biomarkers of neurodegeneration.[41] Proposed mechanisms include impaired cerebral autoregulation, endothelial dysfunction, and cumulative microvascular injury,[42–44] which may interact synergistically with neurodegenerative pathology. Clinically, our findings suggest that long-term BPV may serve as a marker of cognitive risk in the oldest-old, although its interpretation may differ from that in younger populations. BPV may reflect different mechanisms across age groups, with BPV in the very elderly potentially reflecting frailty or impaired physiological regulation rather than solely cardiovascular risk.[45] Notably, prior investigations from *The 90+ Study* and other elderly cohorts have demonstrated that cardiovascular risk factors, including hypertriglyceridemia and late-life onset of hypertension, may be protective with respect to dementia risk,[20,46,47] contrasting with midlife associations.[48,49] From a research perspective, prospective interventional studies with temporally separated BPV and cognitive assessment periods are needed to determine whether BPV is modifiable in very late life and whether targeted therapies can influence cognitive outcomes. Use of continuous or ambulatory BP monitoring, autonomic testing, and neuroimaging markers of cerebrovascular and neurodegenerative disease may help determine whether BPV independently predicts cognitive decline, reflects broader physiological dysregulation, or contributes directly to cerebrovascular and neurodegenerative injury. It is important to note that interventional studies would subsequently be needed to determine whether BPV can be modified safely in very late life and whether such modification improves cognitive outcomes. Such studies may need to prioritize maintaining BP dynamics within an optimal physiological range—preserving cerebral perfusion and adaptability—rather than indiscriminately reducing BPV This approach may have implications for antihypertensive management in the setting of frailty, medical comorbidities, and polypharmacy.[50,51]

Our study has several strengths, including a large, well-characterized cohort of adults 90 years of age and older, cognitive assessments every 6 months, longitudinal follow-up, and advanced statistical modeling of cognitive state transitions. Multi-state models allowed us to capture dynamic transitions between cognitive states, including reversion from cognitive impairment to normal cognition, which occurred with sufficient frequency to warrant explicit modeling. This approach provides a more nuanced view of cognitive aging in

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the oldest-old. The relatively high frequency (≈30%) of observed transitions from cognitive impairment to normal cognition highlights the dynamic and potentially non-linear nature of cognitive trajectories in this population. Such reversions may reflect true biological variability in cognitive function but may also have been influenced by measurement variability and transient factors such as acute illness, medication effects, or fatigue. These findings highlight the importance of accounting for bidirectional transitions when modeling late-life cognitive change and suggest that classifications at a single time-point may not fully capture underlying cognitive trajectories in advanced age.

Several limitations merit discussion. Participants in *The 90+ Study* predominantly self-identified as White (97%) and female (63%) and were well-educated (74% reporting at least some college education), which may limit the generalizability of the results, although these demographics broadly reflect the oldest-old population in the United States.[52] Similarly, findings apply only to individuals who lived to age 90 without dementia, introducing potential survivor bias and limiting applicability to younger populations or those with dementia before study entry. Moreover, individual-level mortality data, including dates of death, were unavailable, precluding explicit modeling of death as a competing event. Consequently, the reported associations reflect the cognitive-state transitions observed while participants remained under follow-up. We were unable to assess short-term BPV, circadian BP patterns, or orthostatic hemodynamics, which may differentially relate to cognitive outcomes. Although models adjusted for baseline hypertension, cardiovascular comorbidities, and BP-modifying medication use, we did not have sufficiently granular longitudinal data on medication dose changes, adherence, treatment intensification, or incident cardiovascular or cerebrovascular events during follow-up. These factors could influence both rSBPV and cognitive decline and may represent sources of residual or time-varying confounding. For example, incident stroke, intercurrent cardiovascular illness, medication nonadherence, or changes in antihypertensive therapy could increase BP variability while also contributing to cognitive decline. Finally, because rSBPV was estimated using BP measurements collected across follow-up, the rSBPV measurement period overlapped with cognitive follow-up. Consequently, we could not establish whether greater rSBPV preceded cognitive transitions, and reverse causation cannot be excluded. Together with the observational study design, this limitation indicates that the findings should be interpreted as longitudinal associations rather than causal effects.

In conclusion, higher long-term rSBPV was associated with worse cognitive outcomes in the oldest-old compared to intermediate rSBPV. These findings suggest that BPV may reflect underlying physiological resilience or vulnerability and warrant further investigation as a potential biomarker—and possibly a modifiable risk factor—in late-life cognitive health.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All human participants or their informants provided written informed consent.

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