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Cognitive & Behavioral Assessment

The association between pulse pressure change and cognition in late life: Age and where you start matters

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Abstract

Introduction: Variations across studies in the association between blood pressure (BP) and cognition might be explained partly by duration of exposure to hypertension and partly by nonrandom attrition over time. Pulse pressure (PP) reflects arterial stiffness which may better reflect chronicity of hypertension.

Methods: Over six annual cycles, 1954 individuals aged 65+ years from a prospective population-based cohort underwent BP measurements and cognitive evaluations. We examined the relationship of change in five cognitive domains to longitudinal PP patterns across the late-life age spectrum, before and after stratifying by baseline systolic blood pressure (SBP) and adjusting for attrition.

Results: There were four longitudinal PP patterns: stable normal, stable high, increasing, and decreasing. Those with lower baseline SBP and an increasing or stable high PP had less decline in cognition, an effect that was attenuated with aging. Among those with higher baseline SBP, there were no differences across PP groups, but increasing age was consistently associated with greater cognitive decline.

Discussion: The effect of PP on cognitive decline depends on age, baseline SBP, and the trajectory of PP change. Cardiovascular mechanisms underlying cognitive aging should be recognized as nuanced and dynamic processes when exploring prevention and treatment targets in the elderly, so that the optimal timing and type of intervention can be identified.

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Keywords: Pulse pressure; Cognitive decline; Heterogeneity

1. Introduction

Despite strong evidence for a positive association between midlife hypertension and late-life cognitive impairment [1–5], the relationship between late-life hypertension and cognitive function remains unclear [1,4,6–8]. Observed inconsistencies between studies partly reflect variations in study design and populations. Another likely factor is unmeasured heterogeneity, within populations, as regard the timing and duration of exposure to hypertension, which in turn could influence its effects and potential modifiability [9]. Such investigations would benefit from a proxy measure representing the duration of exposure to hypertension.

A potential proxy or surrogate measure is pulse pressure (PP), partly reflecting arterial stiffness, measured as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). PP is potentially a better measure of the chronic effects of hypertension than blood pressure itself [1,10–13]. PP increases with age and is associated with a number of cardiovascular risk factors and outcomes [14,15]. Arterial stiffness appears related to Alzheimer disease (AD) pathology, providing a potential vascular marker that is more closely related to AD [13,16–18] than other cardiovascular measures. However, evidence remains conflicted as to the association of cognitive performance with arterial stiffness, whether measured as PP or through ultrasound determined pulse wave velocity [19–24].

Here, we explored the relationships between longitudinal change in PP and cognitive performance in multiple cognitive domains over 5 years and how these relationships were influenced by initial (baseline) blood pressure (BP). We identified subgroups of individuals with distinct PP trajectories over time and compared their relationships with change in cognition over the same period. As an increase in PP typically reflects significant vascular remodeling and stiffening, we hypothesized that those with increasing PP over time would have a greater decline in cognition. Further, because the impact of arterial health on brain health likely varies across the age spectrum of late life, we assessed whether the relationship between change in PP and cognition differed in the young-old and old-old. Finally, we accounted for the potential effects of participant loss over time, which is inevitable and likely nonrandom in longitudinal studies.

2. Methods

2.1. Subjects

The Monongahela–Youghiogheny Healthy Aging Team is an epidemiologic study of cognitive decline and dementia in an age-stratified, random sample drawn from the voter registration list of small town communities in Southwestern Pennsylvania [25]. Details of sampling, recruitment, and cohort characteristics have been previously reported [25]. Inclusion criteria were age 65 or older, not residing in a long-term care facility at study entry, no substantial sensory impairment, and no decisional incapacity. Initial screening was performed on 2036 participants, of whom 54 were excluded from the full evaluation based on substantial baseline cognitive impairment (<21 on age and education-adjusted mini-mental state examination [MMSE]) [26,27]. The full evaluation was conducted on the remaining 1982 participants who had a mean (SD) age of 77.6 (7.4) years; were 61.1% women and 94.8% of mixed European descent; and had a median educational level of high school graduate. For the present analyses, we further excluded another 32 individuals whose full evaluation revealed severe cognitive impairment at study entry, leaving 1954 total participants for the analyses reported here. All

procedures were approved by the University of Pittsburgh Institutional Review Board and all participants provided written informed consent.

2.2. Clinical evaluation

At study entry and each follow-up visit, trained research staff performed comprehensive in-home evaluations including medical history (self-report of diagnosis by health care professional), current and past alcohol and tobacco use, current medications, a brief physical examination, neurologic evaluation, and cognitive testing (see below). At each study visit, blood pressure was measured approximately 90 minutes after the start of the visit by a trained interviewer according to protocol. After the appropriate cuff size was determined, the participant's blood pressure was measured using an aneroid sphygmomanometer and stethoscope. Before the BP reading was taken, the participant was in a seated position for at least 5 minutes with feet flat on the floor. A second reading was taken after having the participant stand for at least 3 minutes. If SBP was >175 mm Hg or DBP was >100 mm Hg in either position, a repeat measurement was performed later in the physical examination. The BP variable used here represents an average of the total measurements taken at each visit.

PP was calculated as SBP-DBP. Participants were classified as hypertensive if they had SBP >140 or DBP >90 or if taking antihypertensive medications. The vascular-related factors included a self-report of physician-diagnosed myocardial infarction, hypertension, congestive heart failure, cardiac related procedures, transient ischemic attack, stroke, diabetes, and elevated cholesterol.

2.3. Cognitive evaluation

The cognitive evaluation consisted of multiple tests in the domains of attention/processing speed, executive function, language, learning and memory, and a single test for visuospatial function. For each domain, a composite Z-score was estimated as the mean of individual Z-scores by test, standardized to raw score means and SDs of the cohort at baseline [25]. Slope of cognitive change in each domain for each individual over time was estimated from a linear mixed model with random intercept and random slope of time.

2.4. Diagnostic category

Using the Clinical Dementia Rating scale (CDR) [28], participants were rated as having no dementia (CDR = 0), possible/very mild dementia (equivalent to mild cognitive impairment; CDR = 0.5), and dementia (CDR ≥1). We restricted the analytic sample at baseline to individuals with CDR <1.

2.5. Statistical methods

See detailed statistical methods in the Supplementary Material.

2.5.1. Trajectories of pulse pressure measurements

We used latent-class random-intercept linear models to identify longitudinal trajectories of pulse pressure (PP) over six annual assessment cycles (including the number of distinct trajectory groups and the trajectory pattern for each group), Fig. 1 (Supplementary Material). Bayesian information criteria were used to determine the number of distinct trajectory groups. Analyses were performed using the package *lcmm* through R v3.1.0.

We compared the PP trajectory groups with regard to baseline demographics, life style/health practices, waist:hip ratio, *APOE* ε4 allele carrier status, and vascular disorders and risk factors using Kruskal–Wallis, chi-square, or Fisher exact tests as appropriate, Table 1. Finally, we assessed the univariable relationships between longitudinally measured SBP and DBP, and change in PP, and patterns of antihypertensive use over the 6 cycles.

2.5.2. Pulse pressure groups and cognitive decline

The median baseline PP in our study cohort was 62 mm Hg, and the median SBP was 132 mm Hg. To explore the association between baseline PP (<62 vs. ≥62 mm Hg) and subsequent slope of change in each cognitive domain, we fit a multivariable linear regression model adjusting for age, education, gender, and baseline cognitive domain score.

Next, to examine the relationship of PP trajectory groups and cognitive decline in each cognitive domain, we fit generalized linear models with normal distribution and identity link, adjusted for age, gender, and education. We lacked sufficient power to include additional covariates because some of the trajectory groups included relatively few participants. Regression parameters were estimated by solving the generalized estimating equations (GEEs). The estimates in the GEE analyses represent the differences in slope between a given PP group and the reference PP group (detailed under Results). Interaction effects of PP groups and age were examined to identify the effects on cognitive decline across the age span. To explore the potential contributions of heterogeneity in the cohort, we repeated the GEE analyses after stratifying the PP groups by baseline SBP according to the group median (≥132 mm Hg vs. < 132 mm Hg). All models included only age as no consistent associations were found with education or gender and cognition.

2.5.3. Attrition

Natural attrition is inevitable in longitudinal observational studies, particularly studies of older adults, and the same cardiovascular risk factors are often associated with PP, cognition, and attrition [29]. To account for possible bias resulting from selective attrition due to death or severe illnesses, we conducted propensity score analyses via
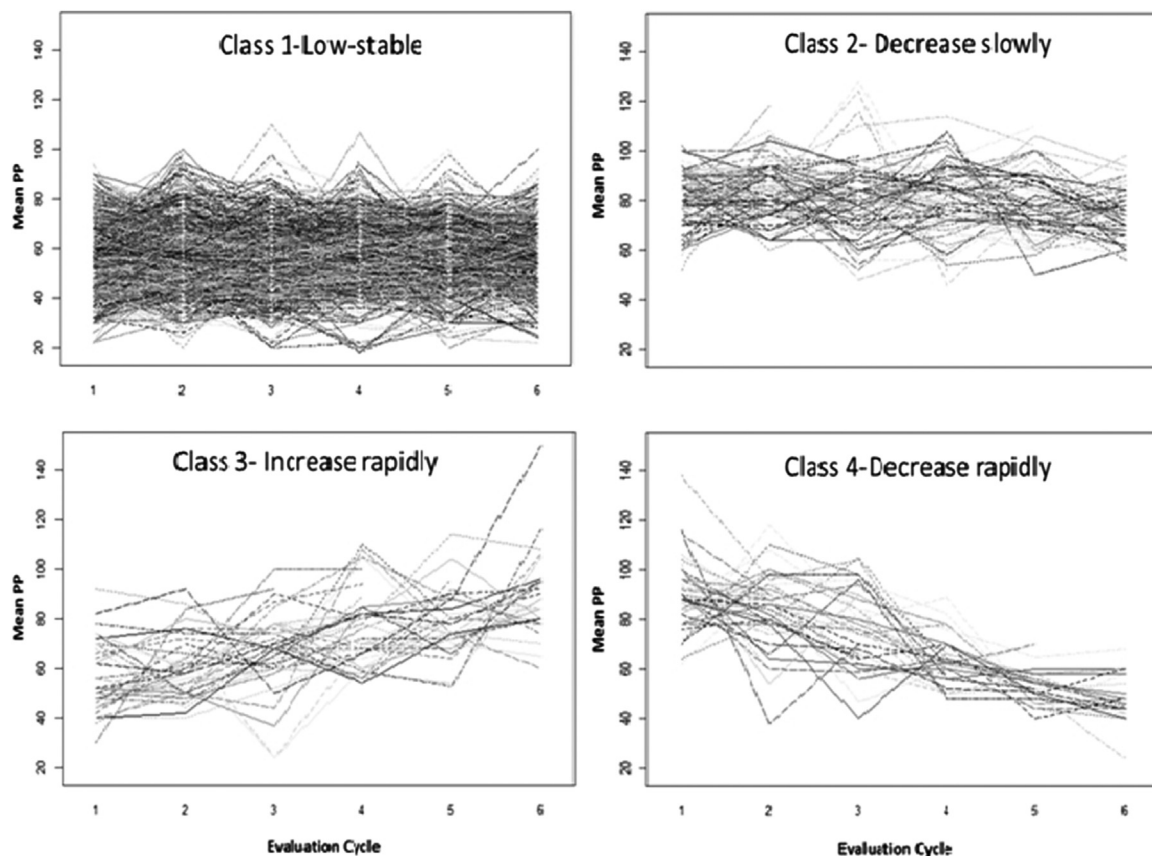

Fig. 1. Class-specific mean latent process predicted trajectory for the four pulse pressure patterns.

Table 1
Descriptive of the four pulse pressure trajectory groups analyses

Baseline variable	PP normal stable (nsPP), n = 1775 Mean (SD); median OR n (%)	PP decreasing slowly (dsPP), n = 96 Mean (SD); median OR n (%)	PP increasing rapidly (irPP), n = 37 Mean (SD); median OR n (%)	PP decreasing rapidly (drPP), n = 46 Mean (SD); median OR n (%)	P value
Age	77.4 (7.4); 78[†§]	79.6 (7.4); 81	76.3 (6.4); 76[#]	81.5 (6.9); 82	<.0001
Age group (y)					.0012
65–74	631 (35.5)[†§]	23 (24.0)	15 (40.5)	7 (15.2)	
75–84	820 (46.2)	44 (45.8)	18 (48.7)	24 (52.2)	
85+	324 (18.3)	29 (30.2)	4 (10.8)	15 (32.6)	
Systolic BP	131.4 (13.7); 130[†§]	153.4 (14.0); 156[‖]	130.3 (17.9); 130[#]	161.2 (17.2); 160	<.0001*
Diastolic BP	74.5 (9.1); 75[§]	72.7 (11.5); 72	74.4 (12.5); 78	70.2 (10.8); 70	.0111
Pulse pressure	56.9 (11.8); 57[†§]	80.8 (10.6); 82[‖]	55.9 (14.3); 52[¶#]	91.0 (15.2); 90	<.0001*
Hypertensive	1115 (63.0)[†]	79 (82.3)	27 (73.0)	36 (78.3)	.0002*
Diabetes	360 (20.3)[†]	36 (37.5)	14 (37.8)	11 (23.9)	<.0001*
Waist-hip ratio	0.902 (0.090); 0.904	0.883 (0.071); 0.876	0.872 (0.075); 0.851	0.879 (0.071); 0.884	.0166
Gender					.0262
Male	705 (39.7)	27 (28.1)	9 (24.3)	15 (32.6)	
Female	1070 (60.3)	69 (71.9)	28 (75.7)	31 (67.4)	
Education					.3464
<HS	231 (13.0)	14 (14.6)	7 (18.9)	11 (23.9)	
=HS	800 (45.1)	45 (46.9)	18 (48.7)	19 (41.3)	
>HS	744 (41.9)	37 (38.5)	12 (32.4)	16 (34.8)	
Race					.9209
Ever smoking	941 (53.2)	46 (47.9)	18 (48.7)	28 (60.9)	.4863
Ever drink					.1999
Stroke	86 (4.9)	4 (4.2)	1 (2.7)	1 (2.2)	.9527
TIA	153 (8.7)[‡]	13 (13.5)	9 (24.3)	6 (13.0)	.0057*
Myocardial Infarction	253 (14.3)	19 (19.8)	8 (21.6)	6 (13.0)	.2901
Congestive heart failure	169 (9.5)	10 (10.4)	2 (5.6)	4 (8.7)	.9149
APOE ε4 allele carrier	329 (20.6)	15 (16.7)	11 (32.3)	10 (24.4)	.2578
Cycle 1 blood pressure					<.0001*
Hypotensive	76 (4.3)[†§]	6 (6.2)[‖]	4 (10.8)[#]	2 (4.3)	
Normotensive	1293 (73.3)[†§]	16 (16.7)[‖]	22 (59.5)[#]	4 (8.7)	
Hypertensive	396 (22.4)[†§]	74 (77.1)[‖]	11 (29.7)[#]	40 (87.0)	
CDR					.0195
0	1293 (72.8)[§]	67 (69.8)	26 (70.3)	24 (52.2)	
0.5	482 (27.2)[§]	29 (30.2)	11 (29.7)	22 (47.8)	

Abbreviation: TIA, transient ischemic attack.

NOTE. As a result of non-normality types of the continuous variables, the Kruskal–Wallis test was performed if the baseline variable is continuous; whereas the chi-square test or Fisher exact test when appropriate was performed otherwise.

*Significance with Bonferroni correction adjusted for multiple comparison (P value < .0083).

[†]C1 vs. C2.

[‡]C1 vs. C3.

[§]C1 vs. C4.

[‖]C2 vs. C3.

[¶]C2 vs. C4.

[#]C3 vs. C4.

logistic regression models evaluated at each cycle to generate time-dependent inverse probability weights. The time-dependent weights were incorporated into the main generalized linear models with GEE to adjust for attrition when evaluating the effects of PP trajectory groups on cognitive changes over time (see Supplementary Material). To better visualize the relationships between PP groups and slope of cognitive decline at different ages, after accounting for attrition, we plotted the predicted slopes for each of the PP groups for 65–74, 75–84 and ≥85 years old, Fig. 2. Analyses were performed using SAS, v9.3 (Cary, NC, USA: SAS Institute, Inc, 2011.).

3. Results

We identified four distinct longitudinal PP trajectories: two relatively stable groups with normal and elevated PP and two with more rapidly increasing and decreasing PP (Table 1 and Fig. 1). We named the first group as normal, stable PP (nsPP) and used it as the reference group for subsequent analyses. We named the remaining groups as low, increasing rapidly PP (irPP), high, decreasing rapidly PP (drPP), and high, decreasing slowly PP (dsPP). Of these four trajectory groups, the drPP group was the oldest and included the largest proportion of participants with
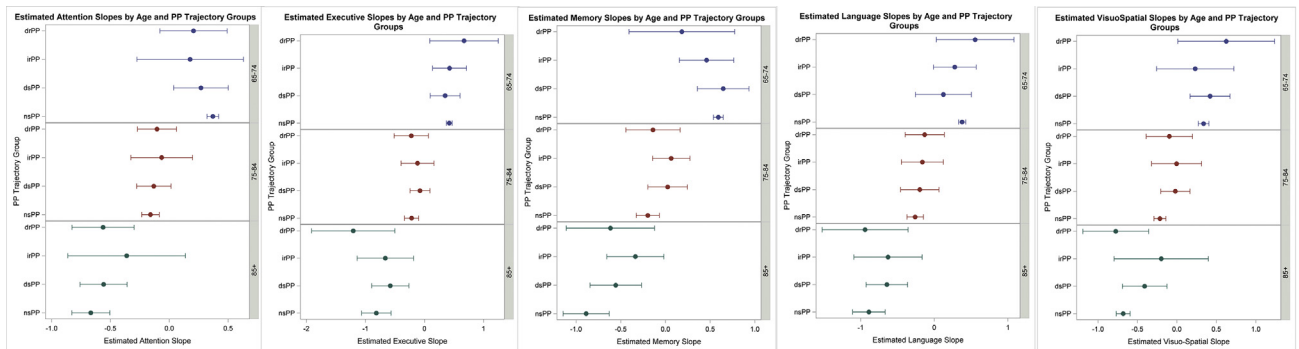
Fig. 2. Estimated cognitive slopes from generalized linear models with GEE adjusting for attrition. The central circle represents the mean slope for the group with the line representing the minimum and maximum for the particular group. The cognitive scores represent the composite Z-score for each domain. The values on the y-axis represent the slope of change over the 6 cycles.

CDR = 0.5. Baseline age, SBP and DBP, waist-hip ratio, gender, history of transient ischemic attack, hypertension, diabetes, and baseline CDR were significantly different among the four groups. Although we identified some associations between the variables that differed between PP groups and with the different cognitive domains, these were not consistent. For that reason, and also the small numbers in some of the PP groups, we did not include these variables in the GLM models using GEE. Higher PP was also significantly associated with greater age, higher SBP, and lower DBP (data not shown).

There was no evidence of increased antihypertensive drug use during this time to explain the rapid decline in SBP and PP (Supplementary Fig. 1). PP changes were associated mostly with SBP changes (as PP increased, SBP increased) rather than DBP changes.

3.1. Baseline PP and cognitive decline over time

Those with low baseline PP (<62 mm) showed greater language decline than those with higher PP (≥62 mm). There were no other significant associations between baseline PP and subsequent slope of cognitive performance, after adjusting for age and education, Supplementary Table 1.

3.2. PP trajectory and cognitive decline over time

Tables 2 and 3 and Fig. 2 show the relationships between pulse pressure trajectory groups and change in cognitive domain scores, over the 6 years, using the generalized linear models with GEE, and accounting for attrition.

A few general observations are summarized here. After stratifying by baseline SBP (threshold: median value of 132 mm Hg), the attrition-weighted GEE models showed distinct patterns of association between PP trajectories and slope of cognitive decline. Among those with baseline SBP below 132, in all domains except language, decline became less steep as PP increased. There was also an age effect such that in older participants, the difference between PP groups was attenuated (as indicated by the negative interaction term of age × PP group). However, among those with

baseline SBP above 132, there were at best marginal associations between PP and slope of cognitive decline (visuospatial function); but as a group, older age was associated with more decline than in the lower SBP group. Not unexpectedly, regardless of baseline SBP, age significantly increased the rate of decline across domains. However, only in those with baseline SBP below the median did we observe an effect of pulse pressure trajectory on cognitive decline. Importantly, these patterns did not emerge in the cohort as a whole before we stratified by baseline BP.

For the following domain-specific results, please refer to Tables 2 and 3 and Fig. 2. All results below refer specifically to the attrition-weighted GEE.

3.3. Attention

Before stratifying by SBP, there were no differences between PP groups. After stratifying the lower SBP group showed less decline in the irPP and dsPP groups, and the higher SBP group had greater decline with age.

3.4. Executive function

Before stratifying, the drPP group had a greater slope of decline, whereas the dsPP group had less decline. After stratifying the lower SBP group showed less executive cognitive decline in both the irPP and dsPP groups. Similar to attention, the higher SBP group had a greater decline with advancing age but no differences between PP groups.

3.5. Memory

Before stratifying, the rapidly increasing (irPP) and dsPP groups showed less memory decline than the reference group. Across all age groups, similar findings were identified for those with lower baseline SBP. Again, those with higher baseline SBP had greater decline in memory function with increasing age.

Table 2
Slope of change over time in cognitive domains among the three PP trajectory groups compared to PP normal stable group (generalized estimating equations adjusting for attrition)

	Parameter estimate (95% CI)	*P* value
Attention		
Intercept	−5.99 (−10.61, −1.38)	.01
Age	**0.18 (0.07, 0.30)**	**.00**
Age × Age	**0.00 (0.00, 0.00)**	**.00**
dsPP	−0.61 (−2.27, 1.05)	.47
irPP	−1.34 (−4.58, 1.91)	.42
drPP	−2.23 (−4.69, 0.23)	.08
Age × dsPP	0.01 (−0.01, 0.03)	.46
Age × irPP	0.02 (−0.02, 0.06)	.40
Age × drPP	0.03 (0.00, 0.06)	.07
Memory		
Intercept	−16.92 (−21.26, −12.57)	.01
Age	**0.27 (0.14, 0.40)**	**.00**
Age × Age	**0.00 (0.00, 0.00)**	**.00**
dsPP	**6.21 (0.00, 12.41)**	**.05**
irPP	**8.18 (2.35, 14.02)**	**.01**
drPP	4.64 (−7.76, 17.03)	.46
Age × dsPP	−0.04 (−0.10, 0.02)	.18
Age × irPP	**−0.06 (−0.11, −0.01)**	**.01**
Age × drPP	−0.04 (−0.13, 0.05)	.39
Language		
Intercept	−2.07 (−5.83, 1.69)	.28
Age	−0.07 (−0.18, 0.05)	.26
Age × Age	0.00 (0.00, 0.00)	.12
dsPP	2.82 (−2.49, 8.13)	.30
irPP	4.12 (−2.53, 10.77)	.22
drPP	0.34 (−6.94, 7.63)	.93
Age × dsPP	−0.03 (−0.08, 0.01)	.17
Age × irPP	−0.04 (−0.09, 0.02)	.23
Age × drPP	−0.01 (−0.07, 0.06)	.87
Executive		
Intercept	−4.25 (−8.60, 0.10)	.06
Age	0.03 (−0.09, 0.15)	.63
Age × Age	0.00 (0.00, 0.00)	.69
dsPP	**6.13 (1.06, 11.20)**	**.02**
irPP	3.74 (−2.25, 9.72)	.22
drPP	**−9.98 (−15.84, −4.11)**	**.00**
Age × dsPP	**−0.05 (−0.09, 0.00)**	**.04**
Age × irPP	−0.05 (−0.10, 0.01)	.08
Age × drPP	**0.07 (0.01, 0.13)**	**.01**
Visuospatial		
Intercept	−1.96 (−9.85, 5.92)	.63
Age	0.02 (−0.17, 0.21)	.86
Age × Age	0.00 (0.00, 0.00)	.68
dsPP	−0.50 (−5.95, 4.95)	.86
irPP	**−6.99 (−14.02, 0.03)**	**.05**
drPP	**−17.14 (−33.64, −0.63)**	**.04**
Age × dsPP	0.02 (−0.03, 0.08)	.35
Age × irPP	0.00 (−0.07, 0.08)	.93
Age × drPP	0.08 (−0.07, 0.22)	.29

Abbreviations: dsPP, decreased slowly; drPP, decreased rapidly; irPP, increased rapidly; nsPP, low-normal stable (reference group).

NOTE. The parameter estimates represent the difference in slopes between specific groups and the reference group (nsPP)—a negative estimate indicates greater decline for that PP group in that cognitive domain over time and a positive estimate indicates less decline. The interaction term between age and PP group indicates whether the difference in slopes between PP groups changes with age—a negative interaction indicates that the difference in cognitive slopes between that PP group and the reference group becomes smaller with increasing age, and a positive interaction indicates such difference becomes larger with increasing age.

3.6. Visuospatial

Before stratifying, the two rapidly changing PP groups, *irPP* and *drPP*, had greater decline in visuospatial performance compared to the reference PP group. After stratifying, the results were the same for the group with higher SBP. However, for the lower SBP group, the *dsPP* group also had greater decline in cognition.

3.7. Language

Language was the only cognitive domain where no differences were identified among PP groups.

4. Discussion

In this prospective study of an elderly, population-based cohort, baseline PP did not predict subsequent cognitive decline over an average of 5 years. However, when evaluating distinct longitudinal profiles of PP change over the same time period and accounting for attrition, we identified differences in cognitive change that (1) varied by trajectory of PP change, (2) varied by cognitive domain, (3) varied by age, between the youngest-old and oldest-old, and (4) was significantly influenced by baseline SBP. Importantly, we found that, after accounting for attrition and baseline SBP, an increasing or persistently high PP was associated with less cognitive decline than in those with low, stable PP but only if baseline SBP was below the median. However, in those starting with higher baseline SBP, it was age, rather than PP group, that influenced cognitive decline the most, with increasing age being associated with greater decline. These findings underscore the importance of identifying the sources of heterogeneity within a population to understand the complex relationships between late life vascular health and cognitive decline and possibly help explain some of the discrepancies in the literature [4,5,8,20–24,30–36]. In particular, they show the importance of looking at dynamic measures of cardiovascular factors, rather than assuming that these variables remain static over time and also of accounting for the individual's own baseline. These findings also reinforce the need for more nuanced approaches to treatment recommendations for cardiovascular disease in the elderly, particularly as they might relate to cognitive health.

There is strong evidence for the association of midlife cardiovascular risk factors and late life dementia. However, the association between late life hypertension and cognition remains unclear [1,7,21,32,37,38]. Notable discrepancies exist among studies of blood pressure and cognition in the elderly, particularly in cross-sectional studies. These

Table 3
Slope of change over time in cognitive domains among the three PP trajectory groups compared to low PP group, stratified by baseline systolic blood pressure (Generalized estimating equations adjusting for attrition)

	Parameter estimate (95% CI)	P value		Parameter estimate (95% CI)	P value
Attention (SBP <132)			Attention (SBP ≥132)		
Intercept	−2.24 (−7.91, 3.41)	.43	Intercept	−4.27 (−9.23, 0.67)	.09
Age	0.01 (−0.14, 0.16)	.87	Age	**0.15 (0.02, 0.27)**	**.02**
Age × Age	−0.00 (−0.00, 0.00)	.84	Age × Age	**−0.001 (−0.002, −0.004)**	**.00**
dsPP	**26.86 (12.11, 41.61)**	**.00**	dsPP	0.23 (−1.65, 2.11)	.81
irPP	**16.53 (6.99, 26.07)**	**.00**	irPP	−0.76 (−7.65, 6.12)	.82
drPP	**−0.28 (−0.44, −0.11)**	**.00**	drPP	−1.44 (−3.80, 0.91)	.22
Age × dsPP	**−0.13 (−0.22, −0.05)**	**.00**	Age × dsPP	−0.00 (−0.02, 0.02)	.80
			Age × irPP	0.00 (−0.07, 0.09)	.86
			Age × drPP	0.01 (−0.01, 0.04)	.22
Executive (SBP <132)			Executive (SBP ≥132)		
Intercept	−6.90 (−12.27, −1.53)	.01	Intercept	−7.05 (−12.10, −1.99)	.00
Age	0.04 (−0.12, 0.21)	.59	Age	**0.22 (0.09, 0.35)**	**.00**
Age × Age	0.00 (−0.00, 0.00)	.99	Age × Age	**−0.001 (−0.002, −0.009)**	**.00**
dsPP	**7.51 (2.68, 12.35)**	**.00**	dsPP	−0.10 (−2.35, 2.13)	.92
irPP	**8.88 (1.27, 16.49)**	**.02**	irPP	0.96 (−4.33, 6.26)	.72
Age × dsPP	**−0.05 (−0.09, −0.01)**	**.01**	drPP	1.63 (−1.76, 5.04)	.34
Age × irPP	**−0.09 (−0.17, −0.02)**	**.00**	Age × dsPP	0.00 (−0.02, 0.03)	.91
			Age × irPP	−0.01 (−0.08, 0.05)	.68
Memory (SBP <132)			Memory (SBP ≥132)		
Intercept	−15.69 (−21.22, −10.17)	.00	Intercept	−19.74 (−25.74, −13.74)	.00
Age	**0.24 (0.08, 0.40)**	**.00**	Age	**0.36 (0.19, 0.53)**	**.00**
Age × Age	**−0.001 (−0.002, −0.000)**	**.04**	Age × Age	**−0.002 (−0.003, −0.007)**	**.00**
dsPP	**16.39 (10.25, 22.53)**	**.00**	dsPP	0.38 (−8.86, 9.64)	.93
irPP	6.37 (−0.39, 13.15)	.06	irPP	**8.91 (0.32, 17.49)**	**.04**
Age × dsPP	**−0.15 (−0.21, −0.08)**	**.00**	drPP	3.63 (−9.16, 16.43)	.57
Age × irPP	−0.05 (−0.11, 0.01)	.13	Age × dsPP	0.00 (−0.06, 0.07)	.95
			Age × irPP	−0.06 (−0.13, 0.003)	.06
			Age × drPP	−0.03 (−0.13, 0.05)	.44
Language (SBP <132)			Language (SBP ≥132)		
Intercept	−1.71 (−8.15, 4.72)	.60	Intercept	−5.20 (−11.06, 0.65)	.08
Age	−0.06 (−0.23, 0.11)	.46	Age	−0.00 (−0.18, 0.18)	.99
Age × Age	0.00 (−0.00, 0.00)	.31	Age × Age	0.00 (−0.00, 0.00)	.70
dsPP	−13.72 (−39.57, 12.12)	.29	dsPP	−0.29 (−13.98, 13.39)	.96
irPP	9.23 (−3.24, 21.71)	.15	irPP	1.14 (−6.69, 8.98)	.77
drPP	0.14 (−0.14, 0.43)	.32	drPP	1.89 (−7.16, 10.95)	.68
Age × dsPP	−0.09 (−0.19, 0.01)	.08	Age × dsPP	−0.00 (−0.10, 0.09)	.91
Age × irPP	−1.71 (−8.15, 4.72)	.60	Age × irPP	0.01 (−0.05, 0.07)	.73
			Age × drPP	−0.01 (−0.09, 0.06)	.68
Visuospatial (SBP <132)			Visuospatial (SBP ≥132)		
Intercept	10.05 (−1.14, 21.25)	.0786	Intercept	−6.34 (−16.39, 3.71)	.21
Age	−0.23 (−0.53, 0.06)	.12	Age	0.15 (−0.10, 0.41)	.23
Age × Age	0.001 (−0.00, 0.003)	.17	Age × Age	−0.00 (−0.00, 0.00)	.17
dsPP	**−11.62 (−20.49, −2.75)**	**.01**	dsPP	−0.69 (−8.20, 6.81)	.85
irPP	5.77 (−0.91, 12.45)	.09	irPP	**−8.18 (−16.02, −0.33)**	**.04**
			drPP	**−19.70 (−39.12, −0.28)**	**.04**
Age × dsPP	0.13 **(0.03, 0.23)**	**.00**	Age × dsPP	0.02 (−0.03, 0.09)	.42
Age × irPP	−0.10 (−0.17, −0.03)	.00	Age × irPP	**0.08 (0.00, 0.15)**	**.03**
			Age × drPP	0.12 (−0.04, 0.28)	.15

Abbreviations: dsPP, decreased slowly; drPP, decreased rapidly; irPP, increased rapidly; nsPP, low-normal stable (reference group).

NOTE. The parameter estimates represent the difference in slopes between specific groups and the reference group (nsPP)—a negative estimate indicates greater decline for that PP group in that cognitive domain over time and a positive estimate indicates less decline. The quadratic term for age indicates a nonlinear trend with age with a negative term indicating an increase in slope with age and a positive term indicating decrease in the slope with age. The interaction term between age and PP group indicates whether the difference in slopes between PP groups changes with age—a negative interaction indicates that the difference in cognitive slopes between that PP group and the reference group becomes smaller with increasing age, and a positive interaction indicates such difference becomes larger with increasing age.

discrepancies may partly reflect the substantial heterogeneity in the timing and duration of experiencing hypertension, within the populations studied. The same baseline BP at study entry could represent a range of durations of prior exposure to hypertension or hypotension, thus exerting a variable impact on longitudinal outcomes of cognition. This variability might explain why hypertension in late life has been associated with an increased or decreased risk of dementia in different studies [37,39]. Using a measure of BP that might reflect the chronicity of hypertension (e.g., PP) is one way of reducing variability in population studies. Examining longitudinal patterns of PP change allowed us to better capture different patterns of prior exposure to hypertension as manifested by arterial stiffness, which would not be possible in cross-sectional studies with a single measure. We were able to explore how changes in PP and cognition relate to each other, in late life and how baseline blood pressure further contributes to this, that is, where you start influences where you are going.

We used PP as it may provide a more informative measure than BP of the degree of cumulative arterial pathology resulting from hypertension and age. Furthermore, PP has been associated with magnetic resonance imaging measures of vascular disease [12,13,15,40], and arterial stiffness has recently been shown to be associated with the presence of cerebral amyloid, increased amyloid deposition over time [17], and CSF and pathologic markers of AD [13,41]. Importantly, changes in PP can occur with isolated changes in either SBP or DBP or with changes in both, with each scenario having different implications. However, in our population, PP changes were associated mostly with SBP changes (as PP increased, SBP increased) rather than DBP changes. This may partially account for the age-related differences that were identified in our population, that is, increasing age was also associated with increasing SBP.

The few studies that have looked at repeated measurements of both BP or arterial stiffness and cognition over time [21,33–36,42] have had varying results. Unlike the Baltimore Longitudinal Study of Aging, we found that an increasing PP was not associated with a greater decline in memory and executive cognitive tests compared to those with a stable, low PP. Rather, in our models, an elevated or increasing PP was associated with less decline in memory, attention, and executive function. This difference could be partly due to our stratifying by baseline SBP. In another study, looking at baseline PP, rather than longitudinal change in PP, there was worsening cognition in both high and low PP in relation to the median quartile group [36]. In a recent study after change in BP in hypertensive patients over 6 years, both increase and decrease in SBP were associated with less decline on the MMSE [30]. Another study examining BP change over 13 years found a decrease in DBP was associated with worse visuospatial performance [5]. But, similar to our findings, those with persistently elevated SBP had no significant worsening over time in any cognitive function. The four PP trajectory groups that

we identified appear to capture the major categories along a spectrum of possible patterns (stable high or low and increasing or decreasing). They also suggest that different pathways to a specific PP level, rather than the PP itself, have distinct implications for cognition. We can only speculate about the potential mechanisms underlying the noted associations between PP and cognition. These results might indicate that with advancing age, which is also associated with an age-related arterial stiffening, that cognitive function, particularly, executive function becomes increasingly reliant on an additional mechanisms such as adequate cardiac output. However, with advancing age and chronic exposure to higher PP this eventually becomes detrimental, as was supported by the findings in those starting with higher SBP. This was supported by a recent study showing that those with previously elevated SBP were at greatest risk for having evidence of regional white matter changes that support executive cognitive function [9].

In the groups with slowly and rapidly increasingly PP, there was a general pattern of less decline in cognitive function that was most pronounced in those starting at lower SBP. Our findings support speculation that an initial elevation in PP might in fact provide some protection against the effects of hypoperfusion on cognition, particularly in the oldest-old. Although elevated PP has been associated with increase cognitive impairment in some studies [33], this has not been a uniform finding [34,36]. Consistent with our study, a recent study assessing the association of arterial stiffness, BP variability, and vascular risk factors in the elderly also found that in those with multiple vascular risk factors an elevated PP was actually protective for cognitive impairment [43]. These results also support calls to liberalize BP goals in the elderly compared to midlife hypertension [31,37,44,45].

Unlike other studies, we explicitly addressed attrition in our cohort, recognizing not only the inevitability of dropout but also the likelihood of the cardiovascular disease and PP being associated with both cognition and dropout. Attrition also highlights the importance of taking into account the impact of those factors associated with dropout in longitudinal, population-based studies. In our case, we found that in the elderly an increasing or persistently elevated PP was actually associated with less cognitive decline. Furthermore, in those starting with higher SBP at study entry, increasing age was associated with less cognitive decline. This could indicate with age that BP treatment goals may have to consider distinct from midlife. Although our data show that the association between PP and cognition clearly varies by age (Fig. 2), follow-up of our own cohort over a longer period of time could reveal the detrimental impact of elevated or rising PP, but the ideal longitudinal study would begin at or before midlife.

There are some limitations worth considering. Although ultrasound methods provide the more direct and precise measure arterial of stiffness, PP measurement is an easy and inexpensively measured surrogate with ready

application to clinical and community settings. In addition, it is important to recognize that the use of manual sphygmomanometer in the elderly may result in "pseudohypertension" that is a result of peripheral artery changes rather than central artery vascular stiffness. It is possible that those with pseudohypertension are overrepresented in the decreasingly rapidly high PP group. If this were the case then decreasing PP could be a result of a change in cardiac output during the study which may differ from other causes of a decrease in PP, but this is speculation. Likewise, a false hypertension has been attributed to the stress of clinic evaluations, that is, white-coat hypertension, but this is unlikely a major issue with this population as all studies are done in home by research staff familiar to the participants. We also recognize that because of the size of our PP groups, we were limited in adjusting for all measures that differed between the groups, Table 1.

5. Conclusions

In our elderly cohort, longitudinal changes in PP and cognition had different relationships that varied by age and cognitive domain and study entry blood pressure. In general, an increasing or higher PP seemed be associated with less cognitive decline in this elderly cohort, particularly in those starting out with lower systolic blood pressure. This work reinforces the need for longitudinal studies in heterogeneous population-based cohorts, ideally using a life-course approach. Our findings point to the possibility that different strategies may be needed for prevention and treatment at different ages. Future studies that identify ideal PP ranges across the aging spectrum may be helpful in further identifying preventative and therapeutic targets.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2016.03.008.

RESEARCH IN CONTEXT

1. Systemic review: Using Pubmed, Google Scholar, and review of research article reference sections we evaluated the current literature for longitudinal associations between pulse pressure and cognition in the elderly with search terms pulse pressure, hypertension, cognitive decline, dementia. Given the dynamic relationship of cardiovascular disease and cognition, we found few studies that examined how change in measures of vascular disease impacted longitudinal cognition. Furthermore, we found few studies that explore the impact of attrition on these relationships—an important consideration in late life epidemiologic studies.

2. Interpretation: We found distinct groups with different trajectories of pulse pressure change with unique relationships to cognitive change. Importantly, we found that the relationship between pulse pressure and cognition differed by age, baseline blood pressure and was significantly impacted by attrition.

3. Future directions: Identifying optimal ranges of pulse pressure that preserve cognition in aging will be critical in identifying prevention and treatment guidelines across the late life age spectrum.

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