Pulse Pressure is Associated with Cognitive Impairment in Japanese Non-Demented Population: A Cross-Sectional Study

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Abstract

Background

Growing evidence suggests that vascular risk factors, especially hypertension, relate not only to cardiovascular disease but also to cognitive impairment. However, the impact of pulse pressure on cognitive function remains controversial. In this study, we evaluated the associations between pulse pressure and cognitive function in a Japanese health examination cohort using propensity matching analysis.

Methods

We examined 2,546 individuals with a mean age of 60.8 ± 10.3 years who voluntarily participated in health examination. Clinical variables including pulse pressure, brain magnetic resonance imaging (MRI), and cognitive function were assessed. We divided the participants into the high and low pulse pressure groups and evaluated their physical examination data, cognitive functions, and silent brain lesions using propensity matching. To clarify whether pulse pressure and blood pressure have different implications for cognitive function, a mediating analysis was also conducted.

Results

Higher pulse pressure corresponded to lower Okabe and Kohs' scores. The relationship between pulse pressure and cognitive impairment was not significantly mediated by systolic blood pressure. We observed no significant associations between silent brain lesions and pulse pressure.

Conclusion

High pulse pressure associates with cognitive impairment without systolic blood pressure mediation in Japanese subjects without dementia.

Introduction

Pulse pressure (PP) is calculated as the difference between systolic (SBP) and diastolic blood pressure (BP) and is considered a measure of arterial stiffness. Recently, high pulse pressure was linked to increased risk of cardiovascular disease [1]. Moreover, because changes in PP can occur in accordance with both systolic and diastolic BP fluctuations, PP might be a more useful than BP for predicting cardiovascular risks [2].

Growing evidence suggests that vascular risk factors, especially hypertension, are related not only to cardiovascular disease but also to cognitive impairment [3]. Since hypertension is a major risk factor for cerebrovascular disease, it may also associate with vascular dementia. The emerging evidence indicates that vascular risk factors are involved in Alzheimer's disease [4], and the association between blood pressure and cognitive impairment was observed in several epidemiological studies [5]. Given that PP is a

better clinical indicator of the functional arterial changes than BP itself, it might be related to the pathogenesis of cognitive impairment. However, the impact of PP on cognitive function remains controversial.

In this study, we evaluated the associations between PP and cognitive function using propensity matching analysis in a Japanese health examination cohort. To clarify whether PP and BP have different implications for cognitive function, the mediation analysis was also conducted.

Methods

Study Population

We studied a total of 2,546 individuals (1,386 men and 1160 women) with a mean age of 60.8 ± 10.3 years (range 27–95). All participants voluntarily underwent the brain health check-up at the Shimane Health Science Center between April 2004 and July 2015. The assessment included medical history, neurological examination by an experienced neurologist, blood pressure, neuropsychological testing, and MRI scans of the head. The criteria for subject exclusion were as follows: any history of neurological or psychiatric conditions, such as cerebrovascular diseases including transient ischemic attack, dementia, depression, or other psychiatric diseases, and missing data. All individuals provided informed consent to participate this study, which was approved by the institutional ethics committee.

Physical examination

During the heath check-up, seated brachial artery systolic and diastolic BP were measured after 15 min of rest. PP was defined as the difference between systolic and diastolic BP. Hypertension was defined as having a systolic BP > 140 mmHg, a diastolic BP > 90 mmHg, or a history of hypertension with antihypertensive therapy. Diabetes mellitus was defined by fasting glucose level exceeding 126 mg/dl, random glucose level exceeding 200 mg/dl, an HbA1c level exceeding 6.5% and/or a medical history of self-reported history of diabetes or treatment with oral antidiabetic drugs or insulin. Dyslipidemia was defined by serum triglyceride level exceeding 150 mg/dl, high-density lipoprotein cholesterol level below 40 mg/dl, or a medical history of dyslipidemia.

Brain imaging

Brain infarction was defined as a focal hyperintense lesion ≥3 mm in diameter on T2-weighted images. Fluid-attenuated inversion recovery images were used to differentiate infarcts from enlarged perivascular spaces. Cerebral microbleeds (CMBs) were defined as homogenous round foci of signal loss on gradient-echo T2*-weighted images that were 2-10 mm in diameter. Periventricular hyperintensities (PVHs) and white matter hyperintensities (WMHs) were evaluated based on their distinct subcortical distributions on fluid-attenuated inversion recovery images. Periventricular hyperintensity (PVH) and subcortical white matter hyperintensity (SWML) were evaluated separately based on their distinct subcortical distributions on the fluid-attenuated inversion recovery image, because PVH was observed adjacent to the ventricles

and SWML was observed separately from the ventricles. PVH was graded on a scale of 0 – 4, as described previously [6]. SWML was graded on a scale of 0 – 3 according to the Fazekas grading scheme [7]. For statistical purposes, PVH and SWML grades were dichotomized; we defined PVH grades 0 – 2 as 'PVH–' and grades 3 – 4 as 'PVH+'; similarly, SWML grades 0 – 1 were defined as 'SWML–', and grades 2 – 3 were termed 'SWML+'. CMBs were identified as 2–10 mm diameter rounded hypointense lesions on T2*-weighted images. All MRI findings were evaluated separately by an experienced neurologist and a radiologist who were blinded to the patients' profiles. When their opinions were inconsistent, a second neurologist was consulted. An interrater study for evaluating MRI lesions was performed blindly by two independent raters.

Cognitive function evaluation

General cognitive function was assessed using Okabe's Intelligence Scale (Okabe's test) [8], which is a shortened and modified Wechsler Adult Intelligence Scale-Revised for the Japanese aged population and includes orientation, semantic memory, calculation, forward and backward digit span, and paired association memory. The test scores a total of 60 points, and its reliability has been previously validated [9]. There was a significant correlation between Okabe's test and the Mini Mental State Examination (MMSE) [8,9]. The Kohs' block design test (Kohs' test) is a popular bedside screening test for constructional function and cognitive function. The subjects were shown cards with a variety of colored designs and were asked to reproduce them using a set of colored blocks, yielding an intelligence quotient [10]. This test assessed the visuospatial ability in addition to executive function. Frontal function was estimated using the frontal assessment battery (FAB) [11]. Affective functions were evaluated using the Self-rating Depression Scale (SDS) [12] and the Japanese version of the Apathy Scale [13].

Statistics

We divided all subjects into the high and low PP groups with a cut-off value of 65 mmHg [14]. To avoid possible confounding effects caused by grouping with PP values, we used propensity score matching in this study. To obtain the propensity score, we assigned these two groups to the explanatory variable and performed logistic regression analysis after correcting for covariates such as age, sex, and medical histories of hypertension, diabetes mellitus, and dyslipidemia. Propensity score matching was performed using the following algorithm: 1:1 ratio nearest-neighbor match with ±0.01 caliper and no replacement. Physical examination results, silent brain lesions, and cognitive functions were compared between the high and low PP groups before and after propensity matching using a two-sided Student's t-test for continuous variables and χ^2 analyses for categorical variables. To evaluate whether the association between PP and cognitive function was affected by systolic BP (SBP), mediation analysis was performed using Sobel. All statistical analyses were performed using IBM SPSS Statistics ver. 22 (SPSS, Inc.). Differences were considered significant at $P < 0.05$.

Results

Physical examination data

Population statistics of the PP groups were characterized before and after propensity matching as presented in Table 1. Among 2,546 participants, 439 (17.2%) were in the high PP group. Individuals in the high PP group were older ($p<0.001$), and were more often females, compared with the low PP group ($p = 0.003$). Subjects with higher PP had hypertension ($p <0.001$) and diabetes ($p <0.001$) significantly more often. However, there was no significant difference in the prevalence of dyslipidemia between the groups. The propensity matching algorithm produced 433 pairs of patients with similar propensities. In the propensity-matched dataset, the systolic and diastolic BP was higher in persons with high PP than in those with low PP ($P <0.05$). There were no statistically significant differences in age, sex, and prevalence of hypertension and diabetes mellitus between the two groups.

Brain imaging results

The prevalence of SBI, PVH, SWML, and CMBs is shown for each group before and after propensity matching in Table 2. Before matching, subjects with higher PP had more SBIs ($p <0.001$) and worse PVH ($p <0.001$) and SWML ($p <0.001$) scores. In the propensity-matched sample, there were no significant differences in the occurrence of silent lesions between the two groups.

Cognitive Functions

The cognitive function scores for the two groups before and after propensity matching are presented in Table 3. Before matching, the high PP group showed lower cognitive function scores in Okabe's test ($p <0.001$), Kohs' test ($p <0.001$), FAB ($p <0.001$), and SDS ($p = 0.014$) compared with the low PP group. After matching, the Okabe scores (especially mental control and digit span) and Kohs' scores were still lower in the high PP group than in the low PP group ($P <0.05$). Apathy scale scores did not show any difference between the groups before and after matching. To investigate whether the relationship between PP and cognitive function was affected by SBP, mediation analysis was performed. As shown in Fig. 1A, the direct effect of PP on Okabe's test was significant (effect size of -0.093), while the SBP mediated effect of PP on Okabe's test was not significant. Similarly, as shown in Fig. 1B, the direct effect of PP on Kohs' test was significant (effect size of -0.312), while the SBP mediated effect of PP on Kohs' test was not significant. Thus, PP was significantly associated with Okabe's and Kohs' tests, but was not mediated by SBP.

Discussion

In this study, we revealed that higher PP associates with cognitive dysfunction. Furthermore, our results indicate that these relationships were not mediated by SBP. However, we observed no significant relationship between PP and silent brain lesions.

Several cross-sectional studies evaluated the relationship between PP and cognitive function. Consistent with our study, Obisesan et al. [15], in a total of 3129 subjects aged ≥ 70 years from the Third National

Health and Nutrition Examination Survey revealed that higher PP was associated with worse MMSE performance. Similarly, Fujihara et al. [16] revealed that in 352 community-dwelling populations, PP associated inversely with cognitive function. Similar relationship between PP and cognitive function have been also demonstrated in longitudinal studies. Peters et al. [17], in a total of 3337 subjects from the HYVET cohort, revealed that higher PP associated with an increased risk of dementia during the 2.2-year of follow-up. Similarly, other studies have revealed that PP predicts cognitive decline in community-dwelling individuals [18,19]. On the other hand, studies in the very old individuals oppose the findings of this study. Molander et al. [20] demonstrated that higher PP related to better cognitive function in a cohort of 476 participants aged 85 years or more. Similarly, Sabayan et al. [21] revealed that higher PP associates with lower annual declines in MMSE scores during the 3.2-year follow-up in the 572-participant cohort of the Leiden 85-plus Study. In the eldest, impaired vascular system function can result in low PP and hypoperfusion in the brain, which in turn may induce cognitive impairment. Further studies are needed to evaluate these age-dependent differences in the relationship between PP and cognitive function.

Interestingly, the relationship between PP and Okabe's and Kohs' tests was not mediated by SBP, even though SBP strongly associated with PP and was previously linked with cognitive dysfunction [22,23]. PP could be a surrogate marker of arterial stiffness [24] that represents the chronic effects of hypertension other than BP itself. Our results are consistent with previous reports showing that PP was a better predictor of cognitive impairment than BP [25,26]. Thus, hypertension-associated changes in the brain might be improved by measures of arterial stiffness, such as PP, rather than SBP. Increased PP might represent diminished regulatory functions of vessels against pulsate blood flow, making the brain tissues more susceptible to direct injury.

In this study, PP was not associated with the prevalence of silent brain lesions, including SBI, PVH, SWML, and CMBs, indicating that PP might affect cognitive function independent of the burden of arteriosclerotic cerebral small vessel-related lesions. In previous reports, the relation between arterial stiffness the amount of Aβ deposition in the brain was suggested [27,28]. A previous study revealed that arterial stiffness measured with peripheral pulse wave velocity significantly associates with the extent of Aβ deposition and the accumulation of Aβ in the brain over 2 years in elderly adults without dementia [27]. Since an increase in PP is recognized as arterial stiffness, it is speculated that increased PP causes decreased flow of brain interstitial fluid, thereby leading to decreased Aβ clearance along the perivascular space [29,30] and accelerating the formation of Aβ plaques.

This study has several limitations. First, the cross-sectional study design limits causal inferences. Second, the subjects were recruited from a health examination cohort that might not properly represent the entire population of Japan. Finally, we could not exclude the possibility of residual confounding by unmeasured determinants, such as medication, diet, or physical activity, which could have an effect on PP.

Conclusion

In conclusion, our findings suggest that PP has a significant relationship with cognitive function among non-demented Japanese individuals. Higher PP was associated with lower general intelligence and visuospatial ability without SBP mediation. Future longitudinal studies are needed to explore the association between PP and cognitive decline in a representative sample of the Japanese population.

Declarations

Ethics approval and consent to participate: All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of Shimane University (No. 20160217-1).

Consent for publication: Not applicable

Availability of data and materials: The raw data associated with this study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: Ryo Mizuhara analyzed and interpreted the data and wrote the manuscript. Shingo Mitaki, Masahiro Takamura, Satoshi Abe, Keiichi Onoda, Shuhei Yamaguchi, and Atsushi Nagai designed the study and prepared the manuscript and supervised the entire study.

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Tables

Table 1. Physical assessment before and after propensity matching

	Before matching			After matching		
	Pulse pressure (mmHg)			Pulse pressure (mmHg)		
Characteristics	Lower (<65)	Higher (≧65)	P value	Lower (<65)	Higher (≧65)	P value
No. of subjects	2017	439		433	433	
Age (year)	59.8 (10.4)	65.4 (8.5)	<0.001	64.9 (8.6)	65.4 (8.4)	0.654
Female (%)	46.6	51.9	0.003	50.3	51.5	0.786
Hypertension (%)	32.0	59.2	<0.001	60.2	58.9	0.729
Diabetes (%)	9.0	14.1	<0.001	13.4	13.6	1.000
Hyperlipidemia (%)	48.3	50.8	0.087	52.0	50.6	0.734
Systolic BP (mmHg)	124.3(14.3)	149.9(14.2)	<0.001	127.5(14.2)	149.9(14.1)	<0.001
Diastolic BP (mmHg)	72.8(11.2)	75.8(11.5)	<0.001	73.7(11.4)	75.9(11.5)	0.004
PP (mmHg)	51.5(8.0)	74.1(7.3)	<0.001	53.9(7.6)	74.0(7.3)	<0.001

Abbreviation: BP□blood pressure. Values are mean (SD).

Table 2. Brain atrophy and silent brain lesions in participants with lower and higher pulse pressure

	Before matching			After matching		
	Pulse pressure (mmHg)			Pulse pressure (mmHg)		
	Lower (<65)	Higher (≧65)	P value	Lower (<65)	Higher (≧65)	P value
SBI	111 (5.3)	45 (10.3)	<0.001	35 (8.1)	45 (10.4)	0.291
PVH grade≧3	119 (5.6)	51 (11.6)	<0.001	49 (11.3)	49 (11.3)	1.000
	398 (18.9)	146 (33.3)	<0.001	127 (29.3)	143 (33.0)	0.271
CMBs	119 (5.6)	32 (7.3)	0.184	44 (9.9)	32 (7.4)	0.186

Abbreviations: SBI, silent brain infarction; PVH, periventricular hyperintensity; SWML, subcortical white matter hyperintensity; CMBs, cerebral microbleeds. Values are n (%).

Table 3. Cognitive functions in participants with lower and higher pulse pressure

	Before Matching			After Matching		
	Pulse pressure (mmHg)			Pulse pressure (mmHg)		
	Lower (<65)	Higher (≧65)	P value	Lower (<65)	Higher (≧65)	P value
Okabe's test (shortened version of WAIS-R)	45.3 (7.1)	42.7 (7.5)	<0.001	44.3 (7.1)	42.7 (7.5)	0.002
Information	16.3 (2.7)	15.9 (2.8)	0.005	16.2 (2.8)	15.9 (2.7)	0.120
Mental control	12.2 (3.8)	11.0 (4.1)	<0.001	11.9 (3.8)	11.1 (4.1)	0.002
Digit span	9.1 (1.3)	8.8 (1.5)	<0.001	9.0 (1.4)	8.8 (1.5)	0.017
Assoc. learning	7.6 (3.1)	7.0 (3.1)	<0.001	7.1 (3.0)	7.0 (3.1)	0.503
Kohs' test	103.0 (18.3)	94.7 (18.1)	<0.001	97.9 (18.0)	95.0 (18.1)	0.019
FAB	16.1 (1.5)	15.6 (1.5)	<0.001	15.8 (1.5)	15.7 (1.5)	0.182
SDS	34.8 (7.5)	33.8 (7.7)	0.014	34.4 (7.9)	33.8 (7.7)	0.256
Apathy scale	11.2 (5.7)	11.2 (5.7)	0.995	10.9 (5.4)	11.2 (5.7)	0.469

Abbreviations: WAIS-R = Wechsler Adult Intelligence Scale-Revised; Assoc. learning Association learning; FAB = frontal assessment battery; SDS = self-rating depression scale. Values are expressed as mean score (SD).

Figures

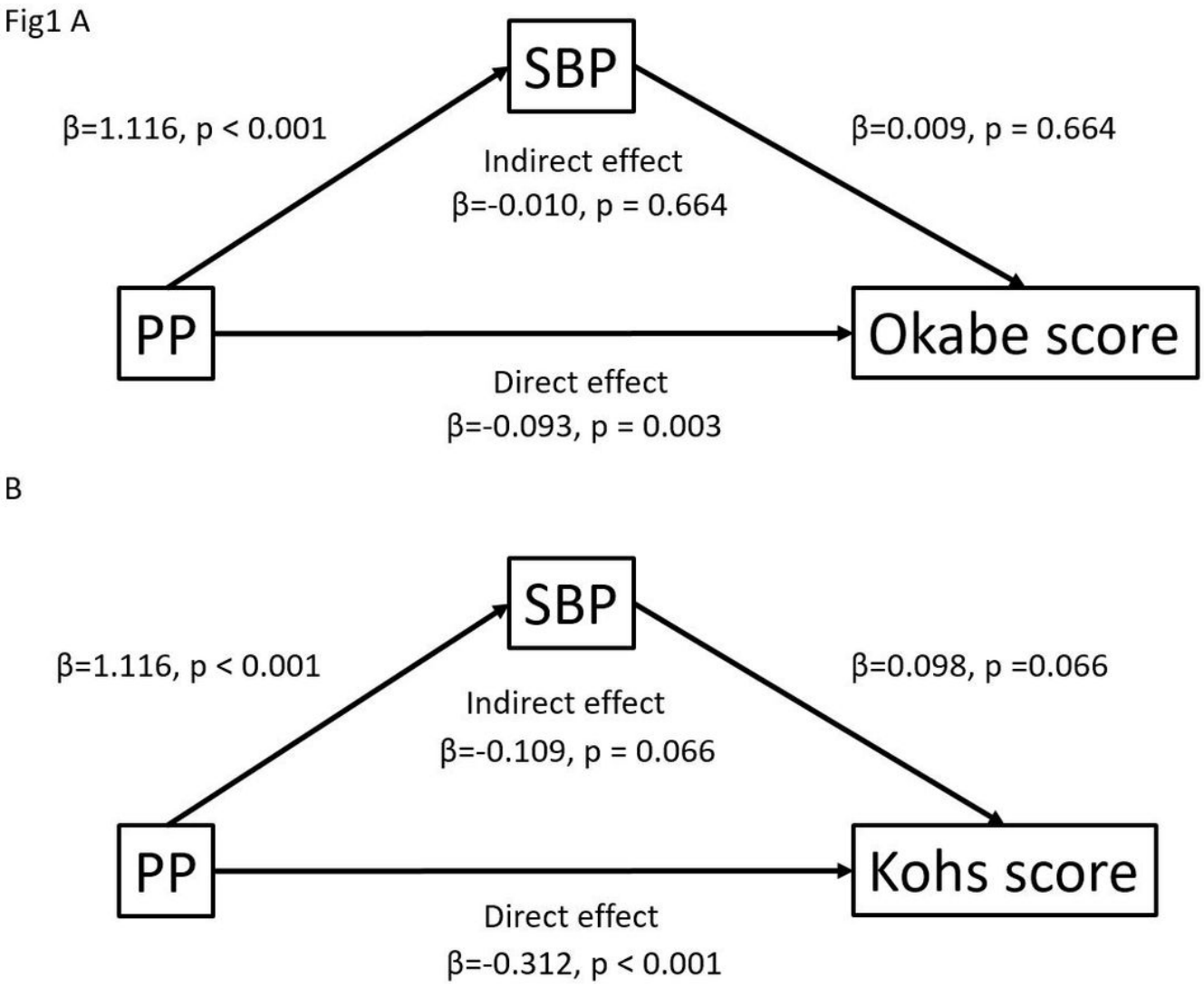

Figure 1

Mediation of the relationship between pulse pressure and cognitive function. A: Measurement of systolic blood pressure mediation in the relationship between pulse pressure and Okabe's test score. B: Measurement of systolic blood pressure mediation in the relationship between pulse pressure and Kohs' test score.