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Visit-to-visit blood pressure variability is associated with arterial stiffness in Chinese adults: A prospective analysis

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Abstract

Blood pressure (BP) variability may have its effect on the development of vascular disease. The authors aimed to examine the association between the visit-to-visit variability (VVV) of BP and arterial stiffness in Chinese adults. The authors included 1407 participants from a prospective cohort study of community residents who were ≥40 years, without a history of myocardial infarction or stroke, and with data at the baseline, the second and the third visits in 2008, 2009, and 2013. The VVV of BP was defined as the standard deviation (SD), the coefficient of variation (CV), the average successive variability (ASV), and the variability independent of the mean (VIM) in BP levels at the 3 visits. Arterial stiffness was measured by brachial-ankle pulse wave velocity (ba-PWV) at the 2nd and the 3rd visits. Levels of ba-PWV change and the occurrence of an elevated ba-PWV increased significantly in the highest tertile of VVV measures of systolic BP (SBP) and pulse pressure (PP) compared with the lowest tertile, respectively. The multivariable regression analysis revealed that VVV measures of SBP and PP were significantly associated with levels of ba-PWV change and the risks of developing an elevated ba-PWV. The odds ratios (ORs) and 95% confidence intervals (CIs) for the risk were 2.12 (1.57–3.12) and 1.92 (1.38–2.68) in participants with the highest versus the lowest tertile of SBP-SD and PP-SD, respectively. No significant association was found for diastolic BP variability measures. The increased long-term variabilities of SBP and PP were associated with an increased risk of arterial stiffness.

Yuwen Zhang and Lizhan Bie contributed equally to this work.

[Correction added on January 30, 2021, after first online publication: The statement "Yuhong Chen and Yu Xu contributed equally to this work" has been changed to "Yuwen Zhang and Lizhan Bie contributed equally to this work".]

1 | INTRODUCTION

Blood pressure (BP) level is strongly associated with stroke, myocardial infarction (MI), and mortality.[1–3] Normal BP, defined as the mean of multiple BP measurements over a period of time, is the most important in the pathophysiology of vascular disease and the basis for recommending optimal BP targets.[1,4] However, average BP cannot fully capture BP-related vascular risk, and changes in BP level have been shown to associate with cardiovascular (CV) events and mortality.[5–7] Although BP variability (BPV) is physiological, it may represent an adaptive humoral and neural response to environmental, behavioral, and emotional stimuli in daily life or may be increased or decreased by antihypertensive treatment.[8] Recently, increasing attention has been paid to the value of visit-to-visit BPV.[9–16]

Visit-to-visit BPV, considered as a long-term BPV, is an intraindividual variation in BP over different clinical visits.[17] Elevated BPV may reflect arterial stiffness and baroreceptor dysfunction, which may be associated with endothelial injury and atherosclerosis and may finally lead to cardiovascular events.[18–21]

Previous studies have mostly focused on the visit-to-visit variability (VVV) of systolic BP (SBP) as the long-term BPV and these studies were conducted in various patient populations such as patients with hypertension,[9,12,17] patients with diabetes,[10,22–24] and patients with a history of other CV disease (CVD) risk factors,[6,25–28] from which findings may not be generalizable to other populations. Moreover, these studies focused on the associations of BPV with clinical CVD events and all-cause mortality. Few studies have investigated the associations of long-term BPV with subclinical atherosclerosis in a general population.[29] Therefore, we used data from a community-based cohort study with several times of BP measurements within years to examine the association between VVV of BP and arterial stiffness measured by brachial-ankle pulse wave velocity (ba-PWV) among Chinese adults aged ≥40 years.

2 | METHODS

2.1 | Study population

Study participants were from an ongoing prospective cohort study, the design of which has been published previously.[30] Briefly, participants were enrolled from a suburban community in Shanghai, China, and underwent 3 examination visits. At the baseline visit (June and July 2008), 10 185 community residents over 40 years or older participated in a screening examination. The fasting plasma glucose (FPG) levels were measured, and participants were divided into three groups accordingly[31]: normal glucose regulation (NGR), with FPG level less than 100 mg/dl and never having diabetes; impaired glucose regulation (IGR), with FPG level of 100 to 125 mg/dl and never having diabetes; and diabetes, with FPG level of 126 mg/dl or greater or a history of diabetes. In the 2nd visit (June through August 2009), participants were randomly selected from the three groups in a ratio of 1.0 (diabetes) to 1.2 (IGR) to 1.44 (NGR). We selected more people with lower blood glucose levels because they might have a lower participation rate than those with higher blood glucose levels. All the selected participants received a comprehensive examination including BP measurement and evaluation of arterial stiffness using ba-PWV. In the 3rd visit (March through May 2013), participants who participated in the 2nd visit were invited to have re-evaluations of BP and ba-PWV. The participation rate in the 3rd visit of those seen at visit 2 was 71.9% (2883/4012).

For the current study, participants with a history of myocardial infarction or stroke prior to the baseline visit (n = 139), participants with missing data for BP at any of the 3 visits (n = 54), with missing data for ba-PWV at the 2nd or the 3rd visit (n = 64), with antihypertensive medications at any of the 3 visits (n = 751), or with ba-PWV level within the highest quartile (≥1618 cm/s) at the 2nd visit (n = 468) were excluded. Eventually, 1407 participants were included for the current analysis (Figure 1).

The study protocol was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiaotong University School of Medicine. All study participants provided written informed consent.

2.2 | Data collection

Detailed information such as demographic and lifestyle factors, medical history, and medication use was obtained through a standard questionnaire administered by trained physicians. The International Physical Activity Questionnaire was used to collect information on participants' physical activities and being physically active was defined by the highest tertile of metabolic equivalent-hours per week.[32] When measuring their height and weight, participants wore lightweight clothes without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured at the level of the umbilicus. BP and heart rate (HR) were measured three times consecutively with 1-min intervals after resting for at least 5 min using an automated electronic device (OMRON Model HEM-752, Omron Company). The mean value of the three measurements was used in analysis. Pulse pressure (PP) was defined as SBP-diastolic BP (DBP). Participants were instructed to avoid alcohol, tea, coffee, and exercise 30 min before BP measurements.

Participants were asked to fast overnight for at least 10 h, and the venous blood samples were collected in the early morning. Plasma concentrations of fasting glucose, serum concentrations of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were measured by an autoanalyzer (ADVIA-1650 Chemistry System, Bayer).

2.3 | Measures of visit-to-visit BPV

Using BP levels at each of the three visits, we calculated the VVV of BP using (1) the standard deviation (SD), (2) the coefficient of

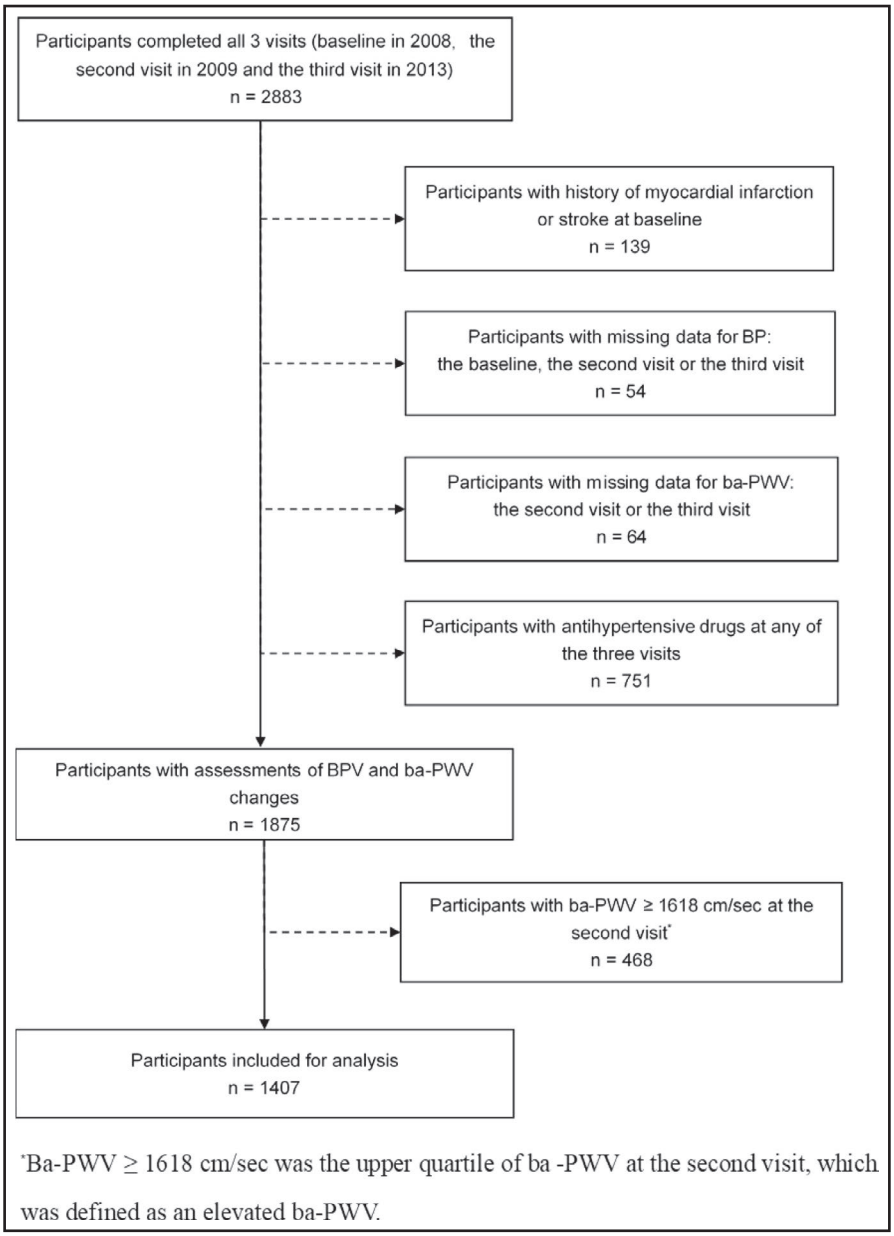


FIGURE 1 Flowchart of the study population

variation (CV), (3) the average successive variability (ASV) defined as the average absolute difference between successive values, and (4) the variability independent of the mean (VIM), which was calculated as $100*SD/mean^{\beta}$, where β is the regression coefficient based on natural logarithm of SD on natural logarithm of mean. All these four metrics have been described in previous studies.[33–35]

2.4 | Measurement of ba-PWV

Participants were required to take 15–30 min of rest before ba-PWV examination. Ba-PWV was measured using the Colin VP-1000 (Model BP203RPEII, form PWV/ABI; OMRON Colin Medical Instruments) as reported previously.[36] Measured with cuffs placed on the upper arms and the ankles, pulse waves were obtained simultaneously from the brachial and tibial arteries. The greater value of the right and the left ba-PWV was used for analysis.

An elevated ba-PWV was defined as a ba-PWV ≥ 1618 cm/s, which was the upper quartile of ba-PWV at the 2nd visit. Ba-PWV change was calculated by abstracting ba-PWV at the 2nd visit from ba-PWV at the 3rd visit. The ratio of ba-PWV change was calculated by dividing ba-PWV change by ba-PWV level at the 2nd visit. The occurrence of an elevated ba-PWV was defined as the proportion of elevated ba-PWV (ba-PWV ≥ 1618 cm/s) at the 3rd visit.

2.5 | Statistical analysis

General characteristics were demonstrated in total participants and according to SBP-SD tertiles. Continuous variables were presented as mean ± SD for normally distributed variables or medians (interquartile ranges) for the skewed variables. We log_{10}-transformed TG to achieve a normal distribution. All the categorical variables were presented as numbers and proportions. We used the ANOVA test to compare continuous variables and the chi-square test to compare categorical variables.

Multiple linear regression models were used to explore the associations of each BPV measure (SD, CV, ASV, and VIM) with the ba-PWV change and ratio of ba-PWV change adjusted for covariates. Four models were used. Model 1 was adjusted for age and sex. Model 2 was further adjusted for education, current smoking, current drinking, and physical activity. Model 3 was further adjusted for baseline WC, DBP/SBP/- (for SBP variability/DBP variability/PP variability, respectively), FPG, log_{10}TG, LDL-c, and HR. Model 4 additionally accounted for average SBP/DBP/PP of the 3 visits (for SBP variability/DBP variability/PP variability, respectively) and ba-PWV at the 2nd visit.

We also used multivariable logistic regression models to evaluate the associations of each BPV measure (SD, CV, ASV, and VIM) with elevated ba-PWV. Tertiles of each BPV measure were used in the models with the lowest tertile as the reference. Similar models were used as the linear regression models except that model 4 did not adjust for ba-PWV at the 2nd visit. Adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated.

Subgroup analyses were performed in participants defined by age, sex, BMI, smoking status, drinking status, diabetes status, and hypertension status. We assessed if there were interactions by adding interaction terms in the adjusted models.

All analyses were performed with the use of SPSS software version 22.0 (SPSS Inc). Significance tests were two-tailed, with a p value < .05 considered as statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of the study population

The baseline demographic and clinical characteristics of the participants across tertiles of SBP-SD are presented in Table 1. Of the 1407 participants included in the study, mean age was 54.7 ± 8.0 years and 36.3% (n = 511) were men. Participants in the highest tertile of SBP-SD were more likely to be older. They had higher levels of baseline WC, PP, FPG, LDL-c, average SBP, DBP, and PP and a lower level of baseline HR.

3.2 | Visit-to-visit BPV and ba-PWV

The ba-PWV change, the ratio of ba-PWV change and the occurrence of an elevated ba-PWV across the SBP, DBP and PP VVV tertiles are shown in Figure 2 and Supplemental Figures S1–S3. They increased significantly across the tertiles of SBP and PP VVV measures. Less evident increase was found across the tertiles of DBP VVV measures.

The multiple linear regression analysis showed that measures of SBP and PP VVV were significantly and independently associated with the ba-PWV change and the ratio of ba-PWV change even after full adjustment for confounders. The associations for DBP VVV measures were not significant or borderline significant (Table 2 and Supplemental Table S1).

We further analyzed the associations between visit-to-visit BPV and the occurrence of an elevated ba-PWV in multivariable logistic regression models. As shown in Table 3 and Supplemental Table S2, when visit-to-visit BPV was examined as a continuous variable in the fully adjusted model (model 4), higher VVV of SBP was significantly associated with an increased risk of developing elevated ba-PWV. Greater VVV of PP was also significantly associated with an increased occurrence of elevated ba-PWV, while no significant association was found for VVV of DBP and the occurrence of elevated ba-PWV. Participants with the highest tertile of SBP-SD had a 1.22-fold increased risk of developing elevated ba-PWV compared with participants with the lowest tertile of SBP-SD after full adjustment (model 4; OR 2.22 [95% CI 1.57–3.12]). The highest tertile of PP-SD conferred an 92% increased risk of developing elevated ba-PWV compared with the lowest tertile of PP-SD (OR 1.92 [95% CI 1.38–2.68]). However, no significant increase in the occurrence of an elevated ba-PWV was found in participants with the highest tertile of DBP-SD compared with those with the lowest tertile of DBP-SD (OR 1.11 [95% CI 0.81–1.53]) (Table 4). Similar results were observed for other measures of VVV (Supplemental Table S3). In addition, we have conducted a sensitivity analysis using the upper quintile of ba-PWV at the 2nd visit (ba-PWV ≥ 1672 cm/s) as the cut-point of elevated ba-PWV and re-did the multivariable logistic regression analysis. Similar findings were observed (Supplemental Tables S4 and S5).

Results for subgroup analysis are shown in Figure 3 and Supplemental Figures S4–S6. Sex, diabetes status, and hypertension status all significantly interacted with SBP VVV measures in association with the risk of developing an elevated ba-PWV, whereas hypertension status had significant interactions with DBP VVV measures and PP VVV measures in association with arterial stiffness (all p for interaction < .05). BP VVV measures were associated with the development of an elevated ba-PWV more closely in participants without hypertension compared with those with hypertension.

4 | DISCUSSION

In the current study, we observed a significant association between the increased VVV of SBP or PP assessed by four indicators (SD, CV, ASV, and VIM) and increased arterial stiffness measured by ba-PWV. The direction and the magnitude of these associations were roughly consistent across measures of SBP or PP variability, and they remained significant even after adjustment for average SBP or average

TABLE 1 Baseline characteristics of study participants by tertiles of SBP-SD

Characteristics	Total	T1 (<6.17 mmHg)	T2 (6.17–10.60 mmHg)	T3 (>10.60 mmHg)	*p* value
Participants, *n*	1407	468	469	470	/
SBP-SD, mmHg	8.26 (5.21–12.03)	4.16 (2.81–5.21)	8.26 (7.20–9.49)	14.02 (12.03–16.85)	/
Age, years	54.7 ± 8.0	53.4 ± 7.4	54.2 ± 7.9	56.4 ± 8.3	<.001
Men, *n* (%)	511 (36.3)	178 (38.0)	166 (35.5)	166 (35.3)	.637
Body mass index, kg/m^2	24.8 ± 3.5	24.7 ± 3.4	24.7 ± 3.6	25.1 ± 3.6	.083
Waist circumference, cm	83.1 ± 9.7	82.7 ± 9.8	82.6 ± 9.8	84.1 ± 9.4	.020
High school education or above, *n* (%)	433 (30.8)	155 (33.1)	147 (31.3)	131 (27.9)	.239
Life style factors, *n* (%)					
Current smoking	363 (25.8)	108 (23.1)	127 (27.1)	127 (27.0)	.256
Current drinking	233 (16.6)	75 (16.0)	83 (17.7)	75 (16.0)	.719
Physically active	462 (32.8)	148 (31.6)	161 (34.4)	152 (32.3)	.612
Heart rate, beats per minute	76.3 ± 10.1	77.2 ± 10.1	76.5 ± 9.9	75.3 ± 10.4	.016
Blood pressure, mmHg					
Systolic blood pressure	123.1 ± 16.2	122.2 ± 14.7	123.1 ± 15.2	124.1 ± 18.5	.181
Diastolic blood pressure	76.6 ± 9.4	76.8 ± 9.0	76.6 ± 9.3	76.6 ± 9.9	.915
Pulse pressure	46.5 ± 11.9	45.4 ± 10.3	46.5 ± 11.5	47.6 ± 13.5	.020
Average blood pressure*, mmHg					
Systolic blood pressure	127.3 ± 14.5	123.2 ± 14.0	126.8 ± 13.3	131.8 ± 14.7	<.001
Diastolic blood pressure	76.4 ± 8.2	75.6 ± 8.3	76.1 ± 8.1	77.5 ± 8.0	.001
Pulse pressure	50.9 ± 11.3	47.7 ± 10.2	50.7 ± 10.7	54.3 ± 12.0	<.001
Fasting plasma glucose, mg/dl	98.9 ± 31.0	96.0 ± 24.5	98.6 ± 31.9	102.0 ± 35.5	.011
Lipid profile, mg/dl					
Triglycerides	117.0 (82.4–171.9)	120.1 (79.7–172.5)	110.75 (81.51–162.14)	118.3 (85.06–181.63)	.202
Total cholesterol	196.5 ± 36.1	194.1 ± 33.9	196.9 ± 39.3	198.5 ± 34.9	.172
High-density lipoprotein cholesterol	54.5 ± 11.5	54.5 ± 11.8	55.1 ± 11.6	53.9 ± 11.2	.244
Low-density lipoprotein cholesterol	94.0 ± 25.6	92.8 ± 25.1	92.8 ± 26.3	96.5 ± 25.3	.033
Diabetes, *n* (%)	243 (17.3)	63 (13.5)	86 (18.3)	63 (13.5)	.023
Hypertension, *n* (%)	366 (26.0)	113 (24.1)	112 (23.9)	141 (30.0)	.054
Ba-PWV at the second visit, cm/s	1300 ± 168	1271 ± 172	1291 ± 171	1338 ± 155	<.001
Ba-PWV at the third visit, cm/s	1556 ± 262	1477 ± 236	1543 ± 241	1649 ± 278	<.001
Ba-PWV change[a], cm/s	256 ± 204	206 ± 181	251 ± 186	311 ± 228	<.001
Ratio of ba-PWV change[b], %	20.1 ± 15.9	16.8 ± 15.0	20.0 ± 15.0	23.6 ± 17.0	<.001
Elevated ba-PWV[c], *n* (%)	501 (35.6)	109 (23.3)	151 (32.3)	240 (51.1)	<.001

Note: Data are baseline characteristics of study participants unless indicated otherwise.

Data are mean ± SD or median (quartile 1-quartile 3) for continuous variables and number (percentage) for categorical variables.

Abbreviations: ba-PWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; SD, standard deviation; T, tertial.

[a]Ba-PWV change was calculated by abstracting ba-PWV at the 2nd visit from ba-PWV at the 3rd visit.

[b]Ratio of ba-PWV change was calculated by dividing ba-PWV change by ba-PWV at the 2nd visit.

[c]Elevated ba-PWV was defined as ba-PWV ≥ 1618 cm/s, which was the upper quartile of ba-PWV at the 2nd visit.

*Average blood pressure was the mean level of blood pressure of the 3 visits.

PP, suggesting that the long-term SBP and PP variabilities may play important roles in the subclinical stage of atherosclerosis in Chinese community adults.

Studies investigating the relationship between visit-to-visit BPV and ba-PWV are rare. Recently, several studies have examined the long-term BPV and found that not only average SBP but also SBP variability is an independent risk factor for atherosclerosis and organ damage in patients with hypertension or other cardiovascular risk factors.[17,28,37,38] Unlike previous studies, our study focused on the association of long-term BPV with subclinical atherosclerosis in the community adults. It should be noted that the study population was a selected sample from the general population because we randomly selected participants with different glycemic status at a 1:1.2:1.44 ratio at the 2nd visit, leading to more participants with diabetes or

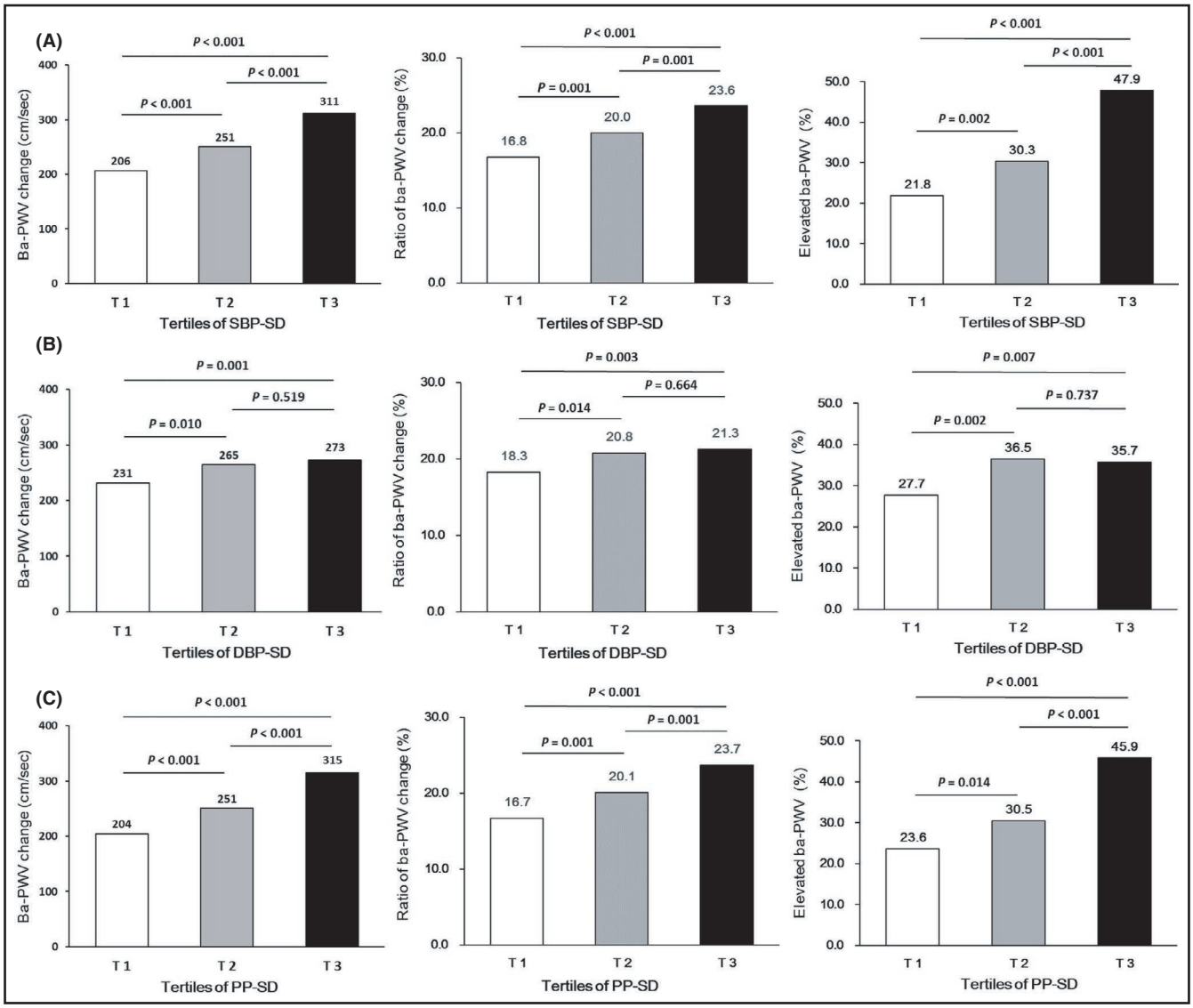


FIGURE 2 (A) Ba-PWV changes and the occurrence of an elevated ba-PWV according to tertiles of SBP-SD. (B) Ba-PWV changes and the occurrence of an elevated ba-PWV according to tertiles of DBP-SD. (C) Ba-PWV changes and the occurrence of an elevated ba-PWV according to tertiles of PP-SD

IGR in the selected sample than the general population. The proportion of the population with impaired glucose regulation at baseline increased, which could make the overall baseline FPG level higher than that of the general population. Considering the effect of higher blood glucose itself on blood vessels, the overall ba-PWV may also be higher than that of the general population. Therefore, we have adjusted both the baseline FPG and ba-PWV at the 2nd visit in the regression analysis. Our findings suggested that the long-term SBP and PP variabilities may play important roles in the development of atherosclerosis at an early and subclinical stage, before a clinical CVD event occurred. This has important clinical and public health implications. Regular monitoring of BP levels is recommended and besides BP levels per se, an evaluation of BPV should also be considered in early prevention of subclinical atherosclerosis.

The mechanism connecting visit-to-visit BPV with vascular damage remains uncertain. Kikuya et al. suggested that increased BPV in elderly and hypertensive patients may be partly due to the increased stiffness and decreased compliance of the large elastic artery caused by aging and hypertension, leading to the decreased function of the pressure reflex.[39] Their study also suggested that disturbed baroreflex function was associated with overpressuring responses to mental and physical stimuli and regulates orthostatic hypotension, postprandial hypotension, and other conditions that lead to increased BPV. Another study suggested that the adverse effects of an increased BPV possibly relate to a greater traumatic effect of wider BP swings on the vessel wall, promoting early target-organ damage.[40] Eto et al. suggested that, independent of average BP, the increase of BPV may contribute to the formation of atherosclerosis in animal models by inhibiting the production of nitric oxide and damaging endothelial function and enhancing the formation of neointima.[41]

Findings from the current study also revealed that compared to individuals with hypertension, individuals without hypertension

TABLE 2 Linear regression analysis of SBP-SD, DBP-SD, and PP-SD associated with the changes of ba-PWV

		Changes of ba-PWV			
		Ba-PWV change (cm/s)		Ratio of ba-PWV change (%)	
Measures of variability		β ± SE	*p* value	β ± SE	*p* value
SBP-SD	Model 1	7.579 ± 0.903	<.001	0.519 ± 0.075	<.001
	Model 2	7.637 ± 0.942	<.001	0.523 ± 0.076	<.001
	[a]Model 3	7.307 ± 0.935	<.001	0.505 ± 0.067	<.001
	[d]Model 4	5.667 ± 0.930	<.001	0.424 ± 0.072	<.001
DBP-SD	Model 1	5.990 ± 1.787	.001	0.418 ± 0.143	.003
	Model 2	6.166 ± 1.791	.015	0.430 ± 0.143	.018
	[b]Model 3	4.260 ± 1.784	.017	0.341 ± 0.144	.018
	[e]Model 4	3.203 ± 1.733	.065	0.229 ± 0.134	.087
PP-SD	Model 1	8.574 ± 1.121	<.001	0.584 ± 0.090	<.001
	Model 2	8.590 ± 1.123	<.001	0.585 ± 0.090	<.001
	[c]Model 3	8.046 ± 1.131	<.001	0.554 ± 0.091	<.001
	[f]Model 4	6.159 ± 1.141	<.001	0.461 ± 0.088	<.001

Note: Model 1 was adjusted for age and sex.

Model 2 was additionally adjusted for education, current smoking, current drinking, and physical activity.

Abbreviations: ba-PWV, brachial-ankle pulse wave velocity; DBP, diastolic pressure; FPG, fasting plasma glucose; HR, heart rate; LDL-c, low-density lipoprotein cholesterol; log_{10}TG, log_{10}-transformed triglycerides; PP, pulse pressure; SBP, systolic blood pressure; SD, the standard deviation; SE, standard error; VVV, visit-to-visit variability; WC, waist circumference; β, regression coefficient.

[a]Model 3 was additionally adjusted for baseline WC, DBP, FPG, log_{10}TG, LDL-c, and HR.

[b]Model 3 was additionally adjusted for baseline WC, SBP, FPG, log_{10}TG, LDL-c, and HR.

[c]Model 3 was additionally adjusted for baseline WC, FPG, log_{10}TG, LDL-c, and HR.

[d]Model 4 was additionally adjusted for average SBP and ba-PWV at the 2nd visit.

[e]Model 4 was additionally adjusted for average DBP and ba-PWV at the 2nd visit.

[f]Model 4 was additionally adjusted for average PP and ba-PWV at the 2nd visit.

TABLE 3 Logistic regression analysis of SBP-SD, DBP-SD, and PP-SD as continuous variables and the development of an elevated ba-PWV

	Model 1		Model 2		Model 3		Model 4	
Measures of variability	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
SBP-SD	1.09 (1.07–1.12)	<.001	1.09 (1.07–1.12)	<.001	1.10 (1.07–1.13)[a]	<.001	1.06 (1.03–1.09)[d]	<.001
DBP-SD	1.06 (1.02–1.10)	<.001	1.06 (1.02–1.11)	.004	1.03 (0.99–1.08)[b]	.193	1.03 (0.98–1.07)[e]	.275
PP-SD	1.11 (1.08–1.15)	<.001	1.11 (1.08–1.15)	<.001	1.11 (1.08–1.14)[c]	<.001	1.07 (1.03–1.10)[f]	<.001

Note: Model 1 was adjusted for age and sex.

Model 2 was additionally adjusted for education, current smoking, current drinking, and physical activity.

Abbreviations: ba-PWV, brachial-ankle pulse wave velocity; CI, confidence internal; DBP, diastolic pressure; FPG, fasting plasma glucose; HR, heart rate; LDL-c, low-density lipoprotein cholesterol; log_{10}TG, log_{10}-transformed triglycerides; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SD, the standard deviation; VVV, visit-to-visit variability; WC, waist circumference.

[a]Model 3 was additionally adjusted for baseline WC, DBP, FPG, log_{10}TG, LDL-c, and HR.

[b]Model 3 was additionally adjusted for baseline WC, SBP, FPG, log_{10}TG, LDL-c, and HR.

[c]Model 3 was additionally adjusted for baseline WC, FPG, log_{10}TG, LDL-c, and HR.

[d]Model 4 was additionally adjusted for average SBP.

[e]Model 4 was additionally adjusted for average DBP.

[f]Model 4 was additionally adjusted for average PP.

TABLE 4 Logistic regression analysis of VVV in SBP-SD, DBP-SD, and PP-SD as categorical variables and the development of an elevated ba-PWV

	OR (95% CI)			
Measures of variability	**Model 1**	**Model 2**	**Model 3**	**Model 4**
SBP-SD				
T1	Reference	Reference	Reference	Reference
T2	1.52 (1.12–2.07)	1.53 (1.12–2.09)	1.62 (1.17–2.24)[a]	1.36 (0.96–1.91)[d]
T3	2.97 (2.20–4.01)	2.98 (2.21–4.03)	3.27 (2.37–4.50)[a]	2.22 (1.57–3.12)[d]
DBP-SD				
T1	Reference	Reference	Reference	Reference
T2	1.53 (1.15–2.05)	1.54 (1.15–2.06)	1.49 (1.09–2.03)[b]	1.51 (1.10–2.06)[e]
T3	1.39 (1.04–1.86)	1.40 (1.04–1.88)	1.11 (0.81–1.53)[b]	1.11 (0.81–1.53)[e]
PP-SD				
T1	Reference	Reference	Reference	Reference
T2	1.49 (1.09–2.03)	1.50 (1.10–2.04)	1.50 (1.09–2.06)[c]	1.54 (1.10–2.14)[f]
T3	2.88 (2.13–3.89)	2.90 (2.14–3.92)	2.80 (2.05–3.82)[c]	1.92 (1.38–2.68)[f]

Note: Model 1 was adjusted for age and sex.

Model 2 was additionally adjusted for education, current smoking, current drinking, and physical activity.

Abbreviations: ba-PWV, brachial-ankle pulse wave velocity; CI, confidence internal; DBP, diastolic pressure; FPG, fasting plasma glucose; HR, heart rate; LDL-c, low-density lipoprotein cholesterol; $\log_{10}$TG, $\log_{10}$-transformed triglycerides; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SD, the standard deviation; VVV, visit-to-visit variability.

[a]Model 3 was additionally adjusted for baseline WC, DBP, FPG, $\log_{10}$TG, LDL-c, and HR.

[b]Model 3 was additionally adjusted for baseline WC, SBP, FPG, $\log_{10}$TG, LDL-c, and HR.

[c]Model 3 was additionally adjusted for baseline WC, FPG, $\log_{10}$TG, LDL-c, and HR.

[d]Model 4 was additionally adjusted for average SBP.

[e]Model 4 was additionally adjusted for average DBP.

[f]Model 4 was additionally adjusted for average PP.

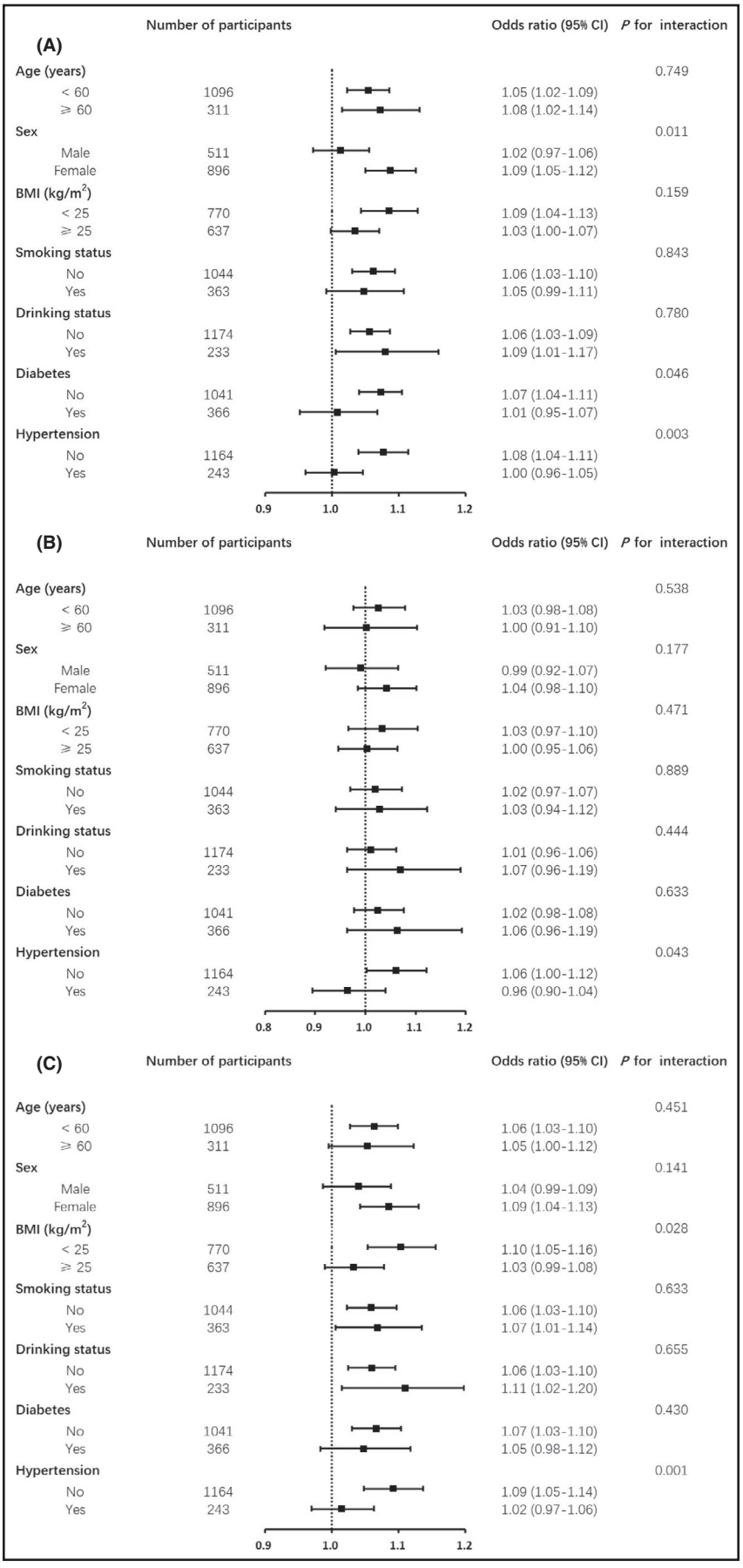
were particularly susceptible to the impact of long-term BPV. One possible explanation is that individuals without hypertension, often with fewer vascular risk factors, are more sensitive to BPV and that, with hypertension, perhaps other risk factors might overshadow the negative influence of BPV. Another possible explanation is that individuals without hypertension, often with lower blood pressure, are more vulnerable to blood pressure variability[42] and that, with higher blood pressure, the contribution of variability is less pronounced.[1,17]

To the best of our knowledge, studies on the association between visit-to-visit BPV and arterial stiffness in the community adults are rare. In addition, because antihypertensive drugs could delay the development of atherosclerosis[43] and interfere with BPV,[44] we excluded individuals with antihypertensive drugs at any of the 3 visits in the current analysis. The current study has several limitations. The long-term BPV was calculated using BP levels at the 3 visits, and ba-PWV was assessed at the 2nd and the 3rd visits. Because BP varies a great deal even in a short period of time, using BP measurements in 1-day time to represent BP levels around one visit could be inaccurate to some extent. Multiple BP measurements over several days around each visit could have provided a more accurate evaluation of the long-term BP variability. A ba-PWV measurement at the baseline visit and a prospective analysis with the assessment of ba-PWV changes after the 3rd visit are needed to better elucidate the potential causal relationship between BPV and arterial stiffness. In addition, the study participants were middle-aged and elderly community residents recruited from suburban Shanghai; therefore, findings from the current study may not be generalizable to people within other age groups or with different socioeconomic or lifestyle background.

5 | CONCLUSIONS

Our findings suggest that a greater visit-to-visit BPV is significantly associated with an increased arterial stiffness, above and beyond the effect of mean BP in the community adults. These findings add to the growing body of evidence on the prognostic value of long-term BPV and highlight the importance of stable BP control in a long term. More prospective studies are needed to further demonstrate

FIGURE 3 (A) Association of SBP-SD with elevated ba-PWV in different subgroups of participants. (B) Association of DBP-SD with elevated ba-PWV in different subgroups of participants. (C) Association of PP-SD with elevated ba-PWV in different subgroups of participants. All models are adjusted for potential confounding factors including age, sex, education, current smoking, current drinking, physical activity, baseline WC, DBP/SBP/-, FPG, $\log_{10}$TG, LDL-c, HR, and average SBP/DBP/PP


(A)
Number of participants
Odds ratio (95% CI)
P for interaction
Age (years) 0.749
< 60 1096 1.05 (1.02-1.09)
≥ 60 311 1.08 (1.02-1.14)
Sex 0.011
Male 511 1.02 (0.97-1.06)
Female 896 1.09 (1.05-1.12)
BMI (kg/m2) 0.159
< 25 770 1.09 (1.04-1.13)
≥ 25 637 1.03 (1.00-1.07)
Smoking status 0.843
No 1044 1.06 (1.03-1.10)
Yes 363 1.05 (0.99-1.11)
Drinking status 0.780
No 1174 1.06 (1.03-1.09)
Yes 233 1.09 (1.01-1.17)
Diabetes 0.046
No 1041 1.07 (1.04-1.11)
Yes 366 1.01 (0.95-1.07)
Hypertension 0.003
No 1164 1.08 (1.04-1.11)
Yes 243 1.00 (0.96-1.05)
0.9 1.0 1.1 1.2
(B)
Number of participants
Odds ratio (95% CI)
P for interaction
Age (years) 0.538
< 60 1096 1.03 (0.98-1.08)
≥ 60 311 1.00 (0.91-1.10)
Sex 0.177
Male 511 0.99 (0.92-1.07)
Female 896 1.04 (0.98-1.10)
BMI (kg/m2) 0.471
< 25 770 1.03 (0.97-1.10)
≥ 25 637 1.00 (0.95-1.06)
Smoking status 0.889
No 1044 1.02 (0.97-1.07)
Yes 363 1.03 (0.94-1.12)
Drinking status 0.444
No 1174 1.01 (0.96-1.06)
Yes 233 1.07 (0.96-1.19)
Diabetes 0.633
No 1041 1.02 (0.98-1.08)
Yes 366 1.06 (0.96-1.19)
Hypertension 0.043
No 1164 1.06 (1.00-1.12)
Yes 243 0.96 (0.90-1.04)
0.8 0.9 1.0 1.1 1.2
(C)
Number of participants
Odds ratio (95% CI)
P for interaction
Age (years) 0.451
< 60 1096 1.06 (1.03-1.10)
≥ 60 311 1.05 (1.00-1.12)
Sex 0.141
Male 511 1.04 (0.99-1.09)
Female 896 1.09 (1.04-1.13)
BMI (kg/m2) 0.028
< 25 770 1.10 (1.05-1.16)
≥ 25 637 1.03 (0.99-1.08)
Smoking status 0.633
No 1044 1.06 (1.03-1.10)
Yes 363 1.07 (1.01-1.14)
Drinking status 0.655
No 1174 1.06 (1.03-1.10)
Yes 233 1.11 (1.02-1.20)
Diabetes 0.430
No 1041 1.07 (1.03-1.10)
Yes 366 1.05 (0.98-1.12)
Hypertension 0.001
No 1164 1.09 (1.05-1.14)
Yes 243 1.02 (0.97-1.06)
0.9 1.0 1.1 1.2

the importance of the long-term BPV in the development of early cardiovascular diseases in diverse populations.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

YZ, LB, YX, and YC had access to all data and take responsibility for its integrity and analysis. YZ and YX conceived the hypotheses and analyses. YZ drafted the paper. YZ and LB provided statistical analysis. YZ, LB, and JZ collected the data. YX and YC revised the manuscript. ML, TW, MX, JL, SW, YB, WW, and GN refined interpretation and the final manuscript. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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