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ORIGINAL RESEARCH

Impact of baseline systolic blood pressure on visit-to-visit blood pressure variability: the Kailuan study

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Background: To investigate the relationship between baseline systolic blood pressure (SBP) and visit-to-visit blood pressure variability in a general population.

Methods: This is a prospective longitudinal cohort study on cardiovascular risk factors and cardiovascular or cerebrovascular events. Study participants attended a face-to-face interview every 2 years. Blood pressure variability was defined using the standard deviation and coefficient of variation of all SBP values at baseline and follow-up visits. The coefficient of variation is the ratio of the standard deviation to the mean SBP. We used multivariate linear regression models to test the relationships between SBP and standard deviation, and between SBP and coefficient of variation.

Results: Approximately 43,360 participants (mean age: 48.2±11.5 years) were selected. In multivariate analysis, after adjustment for potential confounders, baseline SBPs <120 mmHg were inversely related to standard deviation ($P<0.001$) and coefficient of variation ($P<0.001$). In contrast, baseline SBPs ≥140 mmHg were significantly positively associated with standard deviation ($P<0.001$) and coefficient of variation ($P<0.001$). Baseline SBPs of 120–140 mmHg were associated with the lowest standard deviation and coefficient of variation. The associations between baseline SBP and standard deviation, and between SBP and coefficient of variation during follow-ups showed a U curve.

Conclusion: Both lower and higher baseline SBPs were associated with increased blood pressure variability. To control blood pressure variability, a good target SBP range for a general population might be 120–139 mmHg.

Keywords: blood pressure variability, coefficient of variation, standard deviation, systolic blood pressure

Introduction

Blood pressure (BP) variability is defined as the standard deviation or coefficient of variation of beat-to-beat BP obtained by intra-arterial monitoring for 24 hours[1] or non-invasive ambulatory BP monitoring achieved during a period.[2] BP variability included two types: short-term BP variability, which fluctuates during 24 hours (beat-to-beat, minute-to-minute, hour-to-hour, and day-to-night changes) and long-term BP variability, which fluctuates over a longer period (days, weeks, months, seasons, and even years).[3] Previous studies suggested that BP variability is independently associated with the occurrence of hypertensive target organ damage and cardiovascular events,[4–9] as well as the poor prognosis of cardiovascular diseases.[10–13] Controlling the level of BP variability might be a good method to prevent related diseases. Thus, an investigation of the risk factors of BP variability is important and necessary.

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Elevated BP is a major modifiable risk factor for macrovascular diseases (such as coronary heart disease and cerebrovascular events), and is also associated with the progression of microvascular complications.[14,15] Previous studies[16,17] have shown that elevated BP levels can lead to an increase in short-term BP variability. However, few studies have investigated the relationship between BP levels and long-term BP variability, especially in the general population.

In this study, we examined the association between baseline systolic blood pressure (SBP) and visit-to-visit BP variability (ie, BP variations that are reproducible rather than a random phenomenon[18]) in a general population. In addition, we also determined what level of SBP at baseline will have a lower long-term BP variability.

Methods

Study design

The Kailuan study is a prospective cohort study and was conducted in the Kailuan community in Tangshan, Hebei Province, People's Republic of China.[19–21] In total, 101,510 participants (81,110 males; age range, 18–98 years) were enrolled in the Kailuan study from June 2006 to October 2007. The Ethics Committees of both the Kailuan General Hospital and the Beijing Tiantan Hospital approved the study protocol and all participants provided written informed consent.

All participants underwent a clinical examination and a standardized interview, which included questions on smoking and alcohol consumption, socioeconomic parameters, diet, lifestyle, family medical history, physical activity, sleeping time and quality, known diagnosis of arterial hypertension, coronary heart disease, diabetes mellitus, hyperlipidemia and stroke, and current treatment of these diseases. Anthropomorphic parameters (ie, body height, weight, waist and hip circumference) were measured. Body mass index was calculated as the ratio of body weight (in kilograms) divided by the square of body height (in meters). Fasting blood samples were biochemically examined for the concentrations of glucose, high-density lipoproteins, low-density lipoproteins, triglycerides, total cholesterol, and high-sensitivity C-reactive protein.

BP was assessed after the participant had rested for at least 5 minutes. The study participants had refrained from smoking and drinking of coffee, tea, or alcohol for at least 3 hours, and had refrained from any exercise for 30 minutes immediately prior to BP and resting heart rate measurements. BP was measured on the left arm and recorded to the nearest 2 mmHg using a mercury sphygmomanometer under a standard procedure. The average of three readings taken at interval of ≥5 minutes was used in the data analysis. If two of the three measurements differed by >5 mmHg, an additional reading was taken. All the devices that were used to measure the BP and other indices were checked and calibrated by specialized persons. The interview and all examinations were carried out by specially trained medical doctors and nurses.

The study participants were asked to attend a face-to-face interview every 2 years (2008–2009, 2010–2011, and 2012–2013). The follow-up interviews and clinical examinations were performed by hospital physicians, research physicians, or research nurses, who were masked to the results of the previous examinations. In the present investigation, participants who had a history of myocardial infarction, stroke, arterial fibrillation, or any cancer were excluded to avoid bias for these diseases having a great effect on the two main variables of SBP and BP variability. In addition, participants who did not participate in all follow-up examinations or had no SBP data at baseline were included, too.

BP variability was defined as the standard deviation and the coefficient of variation of all values of SBP recorded during the baseline and follow-up visits. The coefficient of variation is the ratio of the standard deviation to the mean SBP.

Statistical analysis

Continuous variables were described by mean (± standard deviation) and categorical variables were described as percentages. To compare the two groups, we used Student's *t*-test or analysis of variance for nonpaired samples of normally distributed parameters and the Wilcoxon or Kruskal–Wallis rank test for nonparametric variables. The chi-square test was applied for the comparison of categorical variables.

We used multivariate linear regression models to test the relationships between SBP and standard deviation, and between SBP and coefficient of variation. We created four multivariate-adjusted models. Model 1 only included the SBP predictor variable. Model 2 adjusted for the potential confounders of age and sex. Model 3 adjusted for the following confounders: age, sex, body mass index, fasting blood glucose, low-density lipoproteins, high-density lipoproteins, total cholesterol, triglycerides, high-sensitivity C-reactive protein, education level, smoking status, drinking status, and physical activity. In addition to the confounders that were adjusted for in model 3, model 4 adjusted for the use of antihypertensive drugs.

We further used multivariate linear regression models to test the relationships between SBP and BP variability by using SBP as a category variable; this was classified into four groups according to the cutoff value of normal BP (SBP <120 mmHg), the high-normal BP values

(SBP 120–139 mmHg), and the clinical classification of hypertension (grade 1 hypertension: SBP 140–159 mmHg; grade 2 and 3 hypertension: SBP ≥160 mmHg). Then we would compare the correlation coefficients and investigate the tendencies in different categories of SBP based on the shape of the relationship between SBP and BP variability showed on the linear chart. Finally, we analyzed the association between an SBP increase of 1 mmHg and BP variability increase in different SBP groups.

Two-sided *P*-values were reported for all analyses. Statistical significance was considered for $P<0.05$. All statistical analyses were performed using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 101,510 subjects who were originally recruited into the Kailuan study, we excluded 5,205 participants who had a history of myocardial infarction (n=1,316), stroke (n=2,014), atrial fibrillation (n=383), or any cancer (n=330); or who had no SBP data at baseline (n=1,162). Then, we excluded 52,945 participants who did not participate in all three face-to-face follow-up examinations (in 2008–2009, 2010–2011, and 2012–2013). Finally, 43,360 participants (32,959 of whom were males) met the inclusion criteria and were eligible for analysis in this study. The mean age was 48.2±11.5 years.

The participants' average SBP, standard deviation, and coefficient of variation in the current study were 128.1±19.7 mmHg, 10.9±5.8 mmHg, and 8.3%±4.0%, respectively. Baseline characteristics of the present study cohort stratified by the four groups of baseline SBP are shown in Table 1. The mean age, body mass index, levels of fasting blood glucose, low-density lipoprotein, high-density lipoprotein, total cholesterol, triglycerides, and high-sensitivity C-reactive protein and the prevalence of physical activity more than four times per week gradually increased with an increase in baseline SBP from group 1 to group 4. However, the number of current smokers and people with a higher education level gradually declined with an increase in baseline SBP.

Table 2 shows the linear regression coefficients of standard deviation and coefficient of variation during the follow-ups from baseline SBP. In all four models of the multivariate linear regression, SBP at baseline was significantly related to the standard deviation and coefficient of variation during follow-up. After adjusting for all potential confounders, including age, sex, body mass index, fasting blood glucose, total cholesterol, low-density lipoproteins,

Table 1 Characteristics of participants according to baseline SBP levels

	Overall	SBP (mmHg)				*P*-value
		<120	120–139	140–159	≥160	
Number of participants	43,360	13,049	18,110	8,368	3,833	
Male, n (%)	32,959 (76.0)	8,645 (66.3)	14,431 (79.7)	6,804 (81.3)	3,079 (80.3)	<0.001
Age (years), mean (SD)	48.2±11.5	43.9±10.9	47.8±11.1	52.4±10.8	55.2±10.2	<0.001
SBP (mmHg), mean (SD)	128.1±19.7	107.7±7.7	126.1±5.8	145.5±5.7	169.2±12.6	<0.001
BMI (kg/m^2), mean (SD)	25.1±3.5	23.9±3.2	25.2±3.4	26.1±3.5	26.6±3.5	<0.001
FBG (mmol/L), mean (SD)	5.4±1.5	5.1±1.2	5.4±1.4	5.6±1.8	5.8±1.9	<0.001
LDL (mmol/L), mean (SD)	2.3±0.9	2.2±0.8	2.3±0.9	2.3±1.0	2.4±1.0	<0.001
HDL (mmol/L), mean (SD)	1.6±0.4	1.5±0.4	1.5±0.4	1.6±0.4	1.6±0.4	<0.001
TC (mmol/L), mean (SD)	4.9±1.1	4.8±1.0	4.9±1.2	5.0±1.2	5.1±1.2	<0.001
TG (mmol/L), mean (SD)	1.7 (1.4)	1.4 (1.1)	1.7 (1.4)	1.9 (1.5)	2.0 (1.6)	<0.001
hs-CRP (mmol/L), mean (SD)	2.3 (6.7)	1.9 (4.8)	2.2 (7.0)	2.6 (7.4)	3.0 (8.6)	<0.001
Current smoker, n (%)	17,677 (40.8)	5,318 (40.8)	7,611 (40.2)	3,325 (39.7)	1,423 (37.1)	<0.001
Current alcohol drinker, n (%)	18,946 (43.7)	5,821 (44.6)	8,202 (45.3)	3,487 (41.7)	1,436 (37.5)	<0.001
Physical activity >4 times/week, n (%)	5,793 (13.7)	1,458 (11.4)	2,251 (12.8)	1,359 (16.9)	725 (19.7)	<0.001
Education level, n (%)						
Illiteracy/primary school	2,809 (6.7)	569 (4.4)	1,104 (6.3)	719 (8.9)	417 (11.3)	<0.001
Middle/high school	36,307 (86.0)	10,611 (82.8)	15,461 (87.6)	7,054 (87.2)	3,181 (86.3)	<0.001
College or higher	3,113 (7.4)	1,636 (12.8)	1,075 (6.1)	314 (3.9)	88 (2.4)	<0.001
Antihypertensive drugs at baseline, n (%)	3,706 (8.9)	208 (1.6)	1,032 (5.9)	1,428 (18.1)	1,038 (29.4)	<0.001
Antihypertensive drugs during follow-ups, n (%)	5,807 (13.4)	525 (4.0)	1,940 (10.7)	1,961 (23.4)	1,381 (36.0)	<0.001
SSD (mmHg), mean (SD)	10.9 (5.8)	10.1±5.2	9.9±5.2	11.9±5.3	16.5±7.3	<0.001
SCV (%), mean (SD)	8.3 (4.0)	8.6±4.0	7.6±3.7	8.4±3.7	10.7±4.8	<0.001

Abbreviations: BMI, body mass index; FBG, fasting blood glucose; HDL, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SCV, coefficient of variation of SBP; SD, standard deviation; SSD, standard deviation of SBP; TC, total cholesterol; TG, triglycerides.

Table 2 Linear regression coefficients of standard deviation and coefficient of variation from baseline SBP

	SSD			SCV		
	β	95% CI	*P*-value	*β*	95% CI	*P*-value
Model 1	0.086	0.083–0.088	<0.001	0.019	0.017–0.021	<0.001
Model 2	0.070	0.068–0.073	<0.001	0.010	0.008–0.012	<0.001
Model 3	0.069	0.066–0.072	<0.001	0.011	0.009–0.013	<0.001
Model 4	0.062	0.059–0.065	<0.001	0.007	0.005–0.009	<0.001

Notes: Model 1 is unadjusted. Model 2 is adjusted for age and sex. Model 3 is adjusted for age, sex, body mass index, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, triglyceride, high-sensitivity C-reactive protein, education level, smoking status, drinking status, and physical activity. Model 4 is adjusted for the same parameters as model 3, with the addition of antihypertensive drugs at baseline and follow-up.
Abbreviations: CI, confidence interval; SBP, systolic blood pressure; SCV, coefficient of variation of SBP; SSD, standard deviation of SBP.

triglycerides, high-sensitivity C-reactive protein, education level, smoking status, drinking status, physical activity, and antihypertensive drugs at baseline and during follow-up, the regression coefficients of standard deviation and coefficient of variation were 0.062 ($P<0.001$) and 0.007 ($P<0.001$), from the baseline SBP, respectively.

Both lower and higher baseline SBP is associated with an increased standard deviation and coefficient of variation (there is a U-shaped relationship). Participants with baseline SBPs of 120–139 mmHg have the lowest standard deviation and coefficient of variation (Figure 1).

To test the relationship between different baseline SBP level groups and standard deviation and coefficient of variation during follow-up, baseline SBP was treated as a categorized variable in the linear regression model. After adjusting for all potential confounders, compared with participants with SBPs of 120–139 mmHg, the coefficients of standard deviation were 0.734, 1.427, and 5.468 for participants with baseline SBPs of <120, 140–159, and ≥160 mmHg, respectively, and the corresponding coefficients of variation were 0.510, 1.234, and 2.487, respectively (Table 3).

To further confirm the relationship between baseline SBP and standard deviation and coefficient of variation during follow-up in the four different baseline SBP level groups, four additional linear regression models, including all potential confounder analyses, were tested, dividing participants into four subgroups. In participants with baseline SBPs of <120 mmHg, the baseline SBP was inversely related to the standard deviation and coefficient of variation during follow-up. In contrast, the baseline SBPs were significantly associated with standard deviation and coefficient of variation in participants with baseline SBPs of ≥140 mmHg (Table 4).

Discussion

In this large prospective cohort study of 43,360 participants in the Kailuan study, baseline SBP was independently associated with visit-to-visit BP variability after controlling for all potential confounders. The relationship between SBP at baseline and BP variability showed a U curve and the participants with the range of 120–139 mmHg of SBP had a lower BP variability at follow-up.

The BP variability reflects the stability condition of BP over a period of time. Although in some studies the predictive value of BP variability for organ damage and incidence of cardiovascular events has shown to be even higher than that of BP itself,[22] BP may affect the BP variability in a short term as well as in a more prolonged term.[23] Previous studies[23,24] have

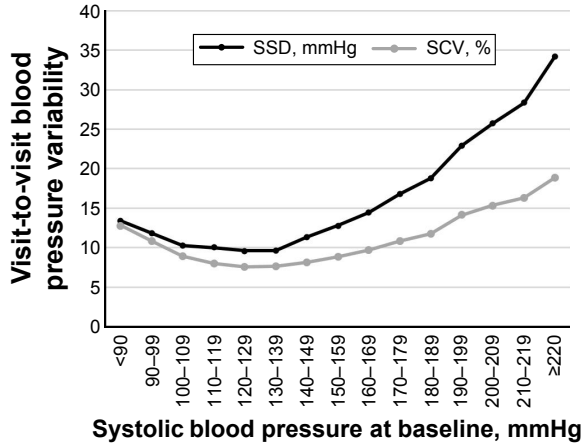

Figure 1 Relationship between systolic blood pressure and visit-to-visit blood pressure variability.
Abbreviations: SCV, coefficient of variation of systolic blood pressure; SSD, standard deviation of systolic blood pressure.

Table 3 Linear regression coefficients of standard deviation and coefficient of variation from different levels of baseline SBP

SBP at baseline (mmHg)	SSD			SCV		
	β	95% CI	*P*-value	*β*	95% CI	*P*-value
<120	0.734	0.607–0.861	<0.001	0.510	0.405–0.615	<0.001
120–139	Reference			Reference		
140–159	1.427	1.283–1.572	<0.001	1.234	1.142–1.327	<0.001
≥160	5.468	5.270–5.666	<0.001	2.487	2.343–2.631	<0.001

Notes: Linear regression model adjusted for age, sex, body mass index, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, education level, smoking status, drinking status, physical activity, and antihypertensive drugs at baseline and follow-up.
Abbreviations: CI, confidence interval; SBP, systolic blood pressure; SCV, coefficient of variation of SBP; SSD, standard deviation of SBP.

Table 4 Linear regression coefficients of standard deviation and coefficient of variation from baseline SBP stratified by different levels of baseline SBP

SBP at baseline (mmHg)	SSD			SCV		
	β	95% CI	*P*-value	*β*	95% CI	*P*-value
<120	–0.155	–0.166 to 0.143	<0.001	–0.173	–0.181 to 0.164	<0.001
120–139	0.028	0.015 to 0.041	<0.001	–0.009	–0.018 to 0.001	0.074
140–159	0.126	0.105 to 0.146	<0.001	0.058	0.043 to 0.072	<0.001
≥160	0.275	0.258 to 0.291	<0.001	0.133	0.122 to 0.145	<0.001

Notes: Linear regression model adjusted for age, sex, body mass index, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, education level, smoking status, drinking status, physical activity, and antihypertensive drugs at baseline and follow-up.
Abbreviations: CI, confidence interval; SBP, systolic blood pressure; SCV, coefficient of variation of SBP; SSD, standard deviation of SBP.

shown that elevated BP levels can lead to an increase in short-term BP variability. Mancia et al reported that hypertension was associated with the BP variability analyzed by beat-to-beat in a short term (24h), and the association was greater so as the hypertension becomes progressively more marked.[23] And then the relationship trend was confirmed existent between mean SBP and visit-to-visit BP variability (relatively long-term) by Muntner et al.[8] To our knowledge, no studies using population-based data have assessed the association between the baseline SBP and visit-to-visit BP variability in a long term.[25] In the present study, we found a U curve relationship between baseline SBP and visit-to-visit BP variability. Participants with baseline SBPs of 120–139 mmHg had a lower long-term BP variability in 6 years of follow-up, compared with baseline SBPs <120 or ≥140 mmHg. The mechanism for this relationship was speculated that the antioscillatory influence of the arterial baroreceptor reflex is impaired[26,27] due to the functional alterations of central and peripheral arteries in subjects with too high or too low BP.[28]

It has been demonstrated that elevated visit-to-visit BP variability is associated with increased all-cause mortality.[8,29,30] Therefore, it is very important to control the long-term BP variability. Previous studies showed that through the potential strategies of adjusting behaviors, controlling large artery stiffening and rationally using antihypertensive drugs to reduce the BP fluctuations between clinic visits could effectively reduce the damage to organs from hypertension and the risk of cardiovascular morbidity.[31] In addition, several studies recommended controlling BP consistently and avoiding large BP differences from one visit to another.[29,32] As suggested by our study, BP controlled at 120–139 mmHg achieved the lowest visit-to-visit BP variability and then optimized cardiovascular protection. The results are consistent with previous studies investigating the association of absolute SBP values and cardiovascular mortality.[17,33] The INVEST study[33] reported that among the patients who had diabetes mellitus and coronary artery disease, the usual control group (baseline SBPs of 130–140 mmHg) had the lowest risk of all-cause mortality compared with the tight control group (baseline SBPs of <130 mmHg) and the uncontrolled group (baseline SBPs of >140 mmHg). In addition, the IDNT[17] study suggested that the risk for cardiovascular deaths and congestive heart failure events was increased in patients with baseline SBPs ≤120 mmHg. Overall, our study further provides evidence from a large Asian cohort that both excessively low and high baseline SBPs would increase the level of long-term BP variability.

This study has several strengths, including the prospective design, the large sample size in an Asian population, enrolment of females and males, standardized evaluation of directly measured BP, and broad assessment of potential confounders. However, our study has some limitations. First, because most of the participants from the Kailuan coalmine were male, the sex distribution of participants was unbalanced. Therefore, this sample cannot be viewed as representative of the Chinese general population. However, studying such a geographically confined and controlled population greatly reduces residual confounding due to diverse socioeconomic factors and lifestyle patterns. Second, some participants who did not attend all three face-to-face follow-up sessions may impact the results in this study. Third, the results of our study were based on a post hoc approach as in the previous studies,[23,24,29] which means that the comparisons of visit-to-visit BP variability on progression have involved nonrandomized groups, Therefore, factors other than those under study may play a role.[29,31] Fourth, during the long period of follow-up, several patients with an early event have been excluded, which may limit the analysis to the later part of the study.[31]

In conclusion, both lower and higher baseline SBPs were associated with an increased visit-to-visit BP variability. To control BP variability, a good target SBP range for a general population might be 120–139 mmHg.

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Disclosure

The authors report no conflicts of interest in this work.

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