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Blood Pressure Trajectories and the Risk of Intracerebral Hemorrhage and Cerebral Infarction: a Prospective Study

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Abstract

The association between long-term blood pressure patterns in community-dwelling adults and risk of intracerebral hemorrhage and cerebral infarction is not well-characterized. This prospective study included 79,385 participants, free of stroke, myocardial infarction and cancer in or prior to 2010(baseline). Systolic blood pressure trajectories were identified using latent mixture modeling with data from 2006, 2008 and 2010. Incident cases of intracerebral hemorrhage and cerebral infarction occurred during 2010 to 2014, confirmed by review of medical records, by three physicians. We identified 5 distinct systolic blood pressure trajectories during 2006 to 2010. Each of the trajectories was labelled according to their blood pressure range and pattern over time: normotensive-stable(n=26,740), prehypertension-stable(n=35,674), stage 1 hypertension-increasing(n=8,215), stage 1 hypertension-decreasing(n=6,422), and stage 2 hypertension-stable(n=2,334). We documented 1,034 incident cases of cerebral infarction and 187 cases of intracerebral hemorrhage. Although the prehypertension-stable trajectory exhibited systolic blood pressure range within the "normal" range(120–140 mmHg) during 2006 to 2010, this group had higher stroke risk relative to the normotensive-stable group(<120 mmHg) (adjusted hazard ratio was 3.11 for intracerebral hemorrhage and 1.99 for cerebral infarction; P<0.001 for both), after adjusting for possible confounders. Individuals in the stage 2 hypertension-stable systolic blood pressure trajectory (175–179 mmHg) had the highest risk of intracerebral hemorrhage(adjusted hazard ratio was 12.4) and cerebral infarction (adjusted hazard ratio was 5.07), relative to the

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normotensive-stable group(P<0.001 for both). Blood pressure trajectories were associated with the risk of stroke and increasing blood pressure trajectories within the currently designated “normal” range may still increase the risk for stroke.

Keywords

blood pressure pattern; trajectory; stroke; infarction; intracerebral hemorrhage

Introduction

Hypertension is an important risk factor for stroke[1] but there is controversy about the definition of hypertension that increases the risk. The American Heart Association guidelines define hypertension as a clinic blood pressure (BP) reading greater than 140/90 mmHg in adults[2]. Recent studies of aggressive BP lowering provided mixed results, the Systolic Blood Pressure Intervention Trial (SPRINT)[3] suggested that achieving norm tension (120/80 mmHg) decreased the cardiovascular risk overall whereas the HOPE-3 trial[4] did not reproduce these findings. Furthermore, a single BP measurement -might not be sufficient for characterizing long-term stroke risk prediction. The change in BP over time is an important risk factor which should be considered[5, 6]. Recently, an assessment of trajectory has been used to reflect long-term BP patterns[7, 8]. Different BP trajectories were associated with altered risk of stroke[9, 10]. However, these studies failed to examine the different stroke subtypes due to small sample size (<10,000).

Patterns of long-term BP changes might have different impact on different stroke subtypes[11, 12]. Although previous studies have shown that the relationship between hypertension and hemorrhagic stroke is stronger than that for ischemic stroke [11, 12], the relationship between the patterns of BP changes over time and the risks of ischemic versus hemorrhagic strokes remains unclear. Intracerebral hemorrhage is a special concern in Asian countries, especially in China[13], as well as the African American and Hispanic populations in the US and elsewhere. A higher percentage of hemorrhagic stroke has been reported in China (~15 to 50%) compared with Western countries [13]. In this context, community-based epidemiological studies in China might be representative of populations elsewhere at relatively high risk for stroke.

Previous studies investigating the association between long-term BP changes between the risks of strokes were limited by small numbers of patients with very few intracerebral hemorrhage cases [14–16].

Although the treatment of hypertension is the clinical norm for stroke risk reduction, hypertension management recommendations for stroke prevention are inconsistent [17]. We hypothesized that multiple trajectory patterns exist within the participants of Kailuan study and that in comparison with a trajectory in which individuals maintain ideal BP levels, a portion of the participants experiences higher levels of BP and/or faster rates of increase in BP that are associated with higher Intracerebral Hemorrhage and Cerebral Infarction risk. We, therefore, investigated the optimal BP trajectories for risk prediction of both

intracerebral hemorrhage and cerebral infarction in a large prospective cohort including ~80,000 Chinese adults with serial BP assessments over time.

Methods

Study design and participants

The Kailuan Study located in Tangshan city, China, is a community based longitudinal cohort study. Study design and procedures have been previously described[18, 19] (Data Supplement Methods S1). In the current analyses, we included 79,385 participants, free of stroke, myocardial infarction and cancer in or prior to 2010 (the baseline), as detailed in Figure S1 and Online Data Supplement Methods S1. There were 2960(3.73%)participants who became lost to follow-ups due to migrations or other reasons. We still included them in the analyses because they contributed person-time, as detailed in the statitiscal analysis section. This investigation was approved jointly by the Ethics Committee of the Kailuan General Hospital and the Human Subjects Committee at Brigham and Women's Hospital/ Harvard Medical School. All the participants gave their written informed consent.

Assessment of blood pressure

In 2006 and during the biennial follow-up, trained nurses and physicians conducted face-to-face surveys[18]. Blood pressure (BP) was measured on the left arm using a mercury sphygmomanometer with a cuff of appropriate size following the standard recommended procedures[20]. Systolic blood pressure(SBP) is the point at which the first of two or more Korotkoff sounds is heard, and the disappearance of Korotkoff sound is used to define diastolic blood pressure (DBP). At least two readings each of SBP and DBP were taken at a 5-minute interval after participants had rested in a chair for at least 5 minutes. The average value of the multiple BP measures was used for further analysis.

Assessment of Intracerebral Hemorrhage and Cerebral Infarction

The outcome was the first occurrence of stroke, either the first nonfatal stroke event, or stroke death. Ascertainment of incident stroke was described previously[18, 19]. Briefly, all participants were linked to the Municipal Social Insurance Institution database and the hospitals' discharge register for incidence of stroke, which cover all the Kailuan study participants. We used the International Classification of Diseases (ICD, I63 for cerebral infarction and I61 for intracerebral hemorrhage), Tenth Revision, for the identification of potential stroke cases. Additional, information regarding past medical history of stroke was collected via questionnaire biennially since 2006. Deaths were collected from local vital statistics offices. For potential stroke cases identified by the ICD code and/or questionnaire, a panel of 3 physicians reviewed their medical records. Nonfatal strokes were defined as the sudden onset of focal neurological deficit with vascular mechanism lasting >24 hours. Fatal strokes were confirmed by medical records, autopsy reports and death certificates with stroke listed as the underlying cause. Stroke was diagnosed according to the World Health Organization criteria[21] combined with a brain computed tomography or magnetic resonance imaging for confirmation. In the current study, we included only 2 main stroke subtypes: intracerebral hemorrhage (not included subarachnoid and subdural hemorrhages) and cerebral infarction.

Assessment of potential confounders was detailed in Data Supplement Methods S2

Statistical analysis

All analyses were conducted using SAS, version 9.3 (SAS Institute, Inc., North Carolina). The person-time of follow-up for each participant was determined from the finishing date of the 2010 survey to either the date of stroke onset, death, lost to follow-up, or the end of follow-up (December 31, 2014), whichever came first.

Because SBP is an independent risk predictor for coronary events, stroke, heart failure, and end-stage renal disease[22–24], we used SBP trajectories as primary exposure in the current study. Latent mixture modeling (PROC TRAJ) was used to identify subgroups that share the similar underlying SBP patterns, irrespectively of whether antihypertensive medications were used. Model fit was assessed using the Bayesian Information Criterion. We initiated a model with 5 trajectories, and then compared the BIC to that with 4, 3, 2, and 1, respectively. The model with 5 trajectories identified fit best.

As secondary exposures, we identified trajectories of diastolic BP (DBP), mid-BP (calculated as [SBP + DBP]/2)[7], mean arterial BP (MAP, calculated as 1/3 SBP + 2/3 DBP), and pulse pressure during 2006 to 2010. We also examined potential effects of cumulative average BP and BP fluctuation (assessed by standard division) during 2006 to 2010, and baseline (2010) BP on future stroke risk. To quantify a linear trend, we assigned the median within each category and modeled this variable continuously, adjusting for aforementioned covariates.

Cox proportional hazards model was used to investigate the association between exposures (e.g., SBP trajectories) and the outcomes, after adjustment for potential confounders, including age, sex, smoking status, alcohol consumption, physical activity, salt intake, income, use of hypoglycemic, antihypertensive, lipid-lowering agents, and aspirin, and average body mass index (BMI), estimated glomerular filtration rate (eGFR), and serum concentrations of total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), and high sensitive C-reactive protein (hs-CRP) during 2006 to 2010. The proportional-hazards assumption was satisfied. As these potential confounders may be change during the follow-up, we did an analysis with all potential confounders updated to the latest follow-up.

Several sensitivity analyses were conducted. Because antihypertensive could change the BP trajectories, we conducted an analysis by excluding 13,280 participants who used any antihypertensive during 2006 to 2010. To examine whether the potential association between SBP trajectories and stroke risk could be explained by any one of the SBP status, we further adjusted the analyses for 2006 or 2010 SBP, one at a time. As BP trajectories could be different between younger and older adults, we modeled trajectories among the younger (< 60 years) and older (≥60 years) participants, separately, and examined their potential impacts on stroke risk. For renal function could be a mediator of the association between BP and stroke, we did a sensitivity analysis in which we did not include the eGFR in the model.

We explored potential interaction between SBP trajectories and age (< 60 years vs. ≥ 60 years), sex, BMI (kg/m^2), smoking (ever vs. never), alcohol consumption (ever vs. never), and diabetes status (yes vs. no).

Result

Five distinct SBP trajectories over a 4-year period were identified (Figure 1). Each of the trajectories were labelled according to their BP range and pattern over time (i.e., stable, decreasing and increasing). Three percent (n=2,334) of participants had SBP consistently >170mmHg (referred to as "stage 2 hypertension-stable pattern"); 8.1% (n=6,422) participants had SBP of approximately 160mmHg in 2006 and decreased during 2006 to 2010, but remained ≥ 140mmHg (referred to as "stage 1 hypertension-decreasing pattern"); 10.4% (n=8,215) participants had SBP of approximately 140mmHg in 2006 and higher during 2006 to 2010, but remained <170mmHg (referred to as "stage 1 hypertension-increasing pattern"); 44.9% (n=35,674) participants had a stable SBP of 120 to 140mmHg (referred to as "prehypertension-stable pattern"); and 33.7% (n=26,740) participants had SBP consistently between 100 and 120mmHg during 2006 to 2010 (referred to as "normotensive-stable pattern"). Individuals with the stage 2 hypertension-stable pattern were more likely to be older and men, have higher salt intake, lower social-economic-status and eGFR, and higher concentrations of TG, CRP, low-density lipoprotein cholesterol (LDL-c), and FBG (Table 1).

During 4 years of follow up (2010 to 2014), we identified 1,034 incident cerebral infarctions and 187 intracerebral hemorrhages. Even though individuals in the prehypertension-stable SBP trajectory subgroup had a SBP that remained in the "normal" range (120–140 mmHg), they still had a significantly higher risk of stroke when compared to individuals in the normotensive-stable SBP trajectory where SBP remained consistently lower than 120 mmHg [adjusted hazard ratio (HR) was 1.99 for cerebral infarction and 3.11 for intracerebral hemorrhage, P<0.001 for both], after adjusting for potential confounders (Table 2). Although individuals with stage 1 hypertension-decreasing SBP pattern had a higher 2006 SBP (164 mmHg) compared to the individuals with the stage 1 hypertension-increasing SBP pattern (143 mmHg), the risks of both subtypes of stroke were lower in these individuals with SBP decreasing overtime, compared with the individuals with SBP increasing overtime (adjusted HR was 3.45 vs. 3.61 for cerebral infarction and 6.79 vs. 9.66 for intracerebral hemorrhage) (Table 2). Further adjustment for 2006 SBP or 2010 SBP, or excluding antihypertensive-users during 2006 to 2010 generated similar results (Table 2).

Adjusted the updated confounders (Table S1), or excluding eGFR from the models (data not shown) did not materially change the results. Similar results were observed when we adjusted for dichotomous variables for presence of diabetes (based on fasting glucose levels and use of hypoglycemic) and dyslipidemia (based on lipid profiles and use of lipid-lowering agents) (date not shown).

The associations between SBP trajectories and stroke risk were more pronounced among those with younger age (age<60 y) or those without diabetes, relative to their counterparts, although the direction of effects were in agreement in the relevant subgroup analyses (Table

S2). Similar results were observed when we used age-specific SBP trajectories, the associations were stronger in younger adults, relative to older adults (Figure S2 and Tables S3&4). We did not find significant interactions between SBP trajectories and sex, BMI, smoking, and alcohol intake in relation to both subtypes of stroke (P-interaction>0.05 for all).

We examined the association of a single SBP in 2010, and average and fluctuation of SBP during 2006 to 2010 with the subtypes of stroke (Table S5). We found that average, rather than a single SBP 120 to 129 mmHg over 4 years was significantly associated with an increased risk for both intracerebral hemorrhage and cerebral infarction. Higher fluctuation in SBP (standard deviation of SBP ≥15.3 mmHg) also significantly associated with both subtypes of strokes (Table S5). Consistently, trajectories of DBP, mid-BP, MAP, and pulse pressure were significantly associated with the risks of both cerebral infarction and intracerebral hemorrhage (Figure S3 and Table S6).

Discussion

We observed heterogeneous BP trajectories in a large prospective cohort of 79,385 participants over a 4-year follow up. Individuals with the stage 2 hypertension-stable SBP trajectory had the highest risk of developing stroke, especially intracerebral hemorrhage – the risk was 12-fold higher relative to those with a consistent SBP <120 mmHg. Moreover, the risks of both cerebral infarction and intracerebral hemorrhage were proportional to the SBP levels. We also modeled trajectories of DBP, mid-BP, MAP and pulse pressure, and generated similar significant results.

The trajectory method combined[25] the average, variability, and the direction of variability to predict the stroke risk. Individuals with stage 1 hypertension-decreasing SBP trajectory had a lower stroke risk compared with individuals with stage 1 hypertension-increasing SBP trajectory, although they had a higher baseline SBP. This result suggests that using a single SBP value to predict stroke risk could misclassify risk groups and the long-term BP changes provide more insight into evolving risk. We also observed blood pressure variability was associated with stroke risk, which agreed with the previous studies[26]. Masked hypertension had higher short-term blood pressure variability than in normotension[27], however, the current study focuses on long-term blood pressure variability and the impact of masked hypertension on long-term blood trajectory remains unknown. Further studies are warranted.

Prolonged exposure to an elevated BP may cause endothelial damage[28] and altered blood cell-endothelium interactions[29], which lead to local thrombi formation and ischemic lesions. Fibrinoid necrosis is considered a pential risk factor for lacunar infarcts through focal stenosis and occlusions[30]. Degenerative changes in endothelial and smooth muscle cells may cause aneurysm formation and predispose for intracerebral hemorrhages. Hypertension also accelerates the atherosclerotic process, increasing the likelihood for cerebral lesions related to stenosis and embolism originating from large extracranial vessels[31]. However, we did not further distinguish subtypes of ischemic stroke in the current study. Moreover, some of the known stroke risk factors, such as left ventricular hypertrophy[32], are related to long-term

elevated BP. Therefore, BP patterns over a longer period of time may better reflect these pathophysiological changes.

Individuals with SBP consistently between 120 and 140mmHg had significantly higher risks of both intracerebral hemorrhage and cerebral infarction than individuals with SBP consistently <120 mmHg, which was consistent with recent meta-analyses[33]. Our results are in concordance that more stringent BP control strategy may be more effective for primary stroke prevention. However, the optimal BP goal for primary stroke prevention remains unclear. In the SPRINT comparing a more intensive BP (target SBP < 120mmHg) control strategy with the standard BP control (target SBP < 140mmHg) in a non-diabetic cohort, intensive BP control strategy resulted in lower rates of major cardiovascular events and total mortality[3]. However, the SPRINT did not show a significant stroke risk reduction with a lower SBP goal which might due to small numbers of stroke cases in this cohort. In another trial based on 4,733 participants with type 2 diabetes,[34] a target SBP of <120 mmHg vs <140 mmHg was associated with a reduced risk of total stroke (HR 0.59, 95% CI 0.39 to 0.89). A meta-analysis including 11 studies, reported that compared with standard SBP control (SBP 130 to 149 mmHg), tighter BP control (SBP <130 mmHg) led to substantial stroke risk reduction[35]. Another recent meta-analysis of 19 RCTs showed that patients in the more intensive BP-lowering treatment group (mean BP 133/76 mmHg) had a 22% stroke risk reduction compared with patients in the less intensive BP-lowering treatment group (mean BP 140/81 mmHg)[36]. Although meta-analyses supported a more stringent BP control strategy, different studies using different BP cut-offs, and the optimal BP target remains unclear. Meta-analyses are also limited by post-hoc analyses and different criteria chosen for trial selections. Furthermore, majority of intervention studies included only people with hypertension and followed for a relatively short-term period, which may limit the generalizability of their results to general population without hypertension. Current hypertension treatment guidelines are somewhat confusing likely due to lack of clear evidence. The 2013 European Society of Hypertension/European Society of Cardiology BP management guideline recommended lower SBP below 140 mmHg and DBP below 90 mmHg, but the strength of the recommendation is Class IIA and the level of evidence is B[37]. The current recommendations from the panel appointed to the Eighth Joint National Committee guidelines recommended to BP goal of 150/90 mmHg in people older than 60 years to reduce the risk of “stroke, heart failure, and coronary heart disease[38] although the subject is still under debate[39].

Consistently, we observed that the association between BP trajectories and future stroke risk was stronger among younger adults, relative to those aged 60 years or older. We also found that the impact of SBP on stroke risk appeared to be weaker among individuals with diabetes, relative to those without diabetes. This is consistent with our previous findings that BP goal in diabetic population could be different than that in nondiabetic population[18]. These together suggested that guidelines regarding the optimal BP goal for primary stroke prevention could be different across different populations.

Because intracerebral hemorrhage only represents a small percentage of total stroke cases, especially in developed countries, it is difficult to study how hypertension contributes to the risk of intracerebral hemorrhage specifically and what is the optimal BP goal for its primary

prevention. In the ACCORD (The Action to Control Cardiovascular Risk in Diabetes) and SPRINT trials, only the total numbers of stroke cases were reported and the specific incidences of cerebral infarction verses intracerebral hemorrhage in the two interventional groups were not characterized[3, 34]. We took the advantage of our large prospective cohort and observed a strong association between SBP trajectories and the risks of intracerebral hemorrhage, which is more pronounced than cerebral infarction. Even maintaining SBP with normotensive range of 120 to 140 mmHg, the risk of intracerebral hemorrhage was still three times of those whose SBP remain below 120 mmHg. Currently, randomized controlled trails' data regarding optimal BP goal for primary intracerebral hemorrhage prevention are lacking. In the secondary Prevention of Small Subcortical Strokes trial including 3020 participants with prior lacunar infarctions, individuals in the low BP target group (SBP < 130 mmHg), the rate of intracerebral hemorrhage was reduced by two-thirds compared with the higher-target group (SBP 130 to 149 mmHg)[40], indicating that a more stringent BP control strategy might be more beneficial.

One limitation of our study is that we only included Chinese adults living in the Kailuan community. The trajectories identified in these participants may not be generalizable to other populations. However, the homogeneous nature of our cohort may help to reduce potential confounding factors because racial and healthcare disparities and enhance internal validity. The large number of intracerebral hemorrhage cases identified in our participants may also provide insight regarding how hypertension contributes to its risk and optimal prevention strategy. Because only a relatively small number of women (n=17,374) was included in the current study, we may not have statistical power to detect the potential sex-difference in the association between BP trajectories and stroke risk. Another limitation is that we did not differentiate the location of the intracerebral hemorrhage and did not further distinguish subtypes of ischemic stroke. Previous studies have shown that hypertension is related to both lobar and non-lobar intracerebral hemorrhages, particularly in non-lobar intracerebral hemorrhage[11], although these studies were limited to either a retrospective design or very few case numbers. The relative risks for each subtype of intracerebral hemorrhage related to hypertension need further investigation.

Perspectives

In summary, our study observed different BP trajectories exist in the Kailuan study participants and these trajectories were associated with future stroke risk. Monitoring trajectories of BP may provide an important approach to identify population with higher risk of stroke and help to prevent stroke. Future research needs to explore the key risk factors of the elevated BP trajectories. Data from large well-designed RCTs are needed to further confirm the optimal BP management strategies in primary prevention for both intracerebral hemorrhage and cerebral infarctions, and their subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New

We identified five distinct blood pressure trajectories during 2006 to 2010.

Blood pressure trajectories were associated with the risk of stroke and increasing blood pressure trajectories within the currently designated “normal” range may still increase the risk for stroke.

What Is Relevant

Individuals in the prehypertension-stable trajectory exhibited SBP range within the “normal” range (120–140 mmHg) during 2006 to 2010 had higher stroke risk relative to the normotensive-stable group(<120 mmHg), relative to the normotensive-stable group.

Individuals in the stage 2 hypertension-stable SBP trajectory (mean SBP 175–179 mmHg) had the highest risk of intracerebral hemorrhage and cerebral infarction, relative to the normotensive-stable group.

Summary

We identified five distinct blood pressure trajectories and found that these patterns were significantly associated with the risks of developing both cerebral infarction and intracerebral hemorrhage.

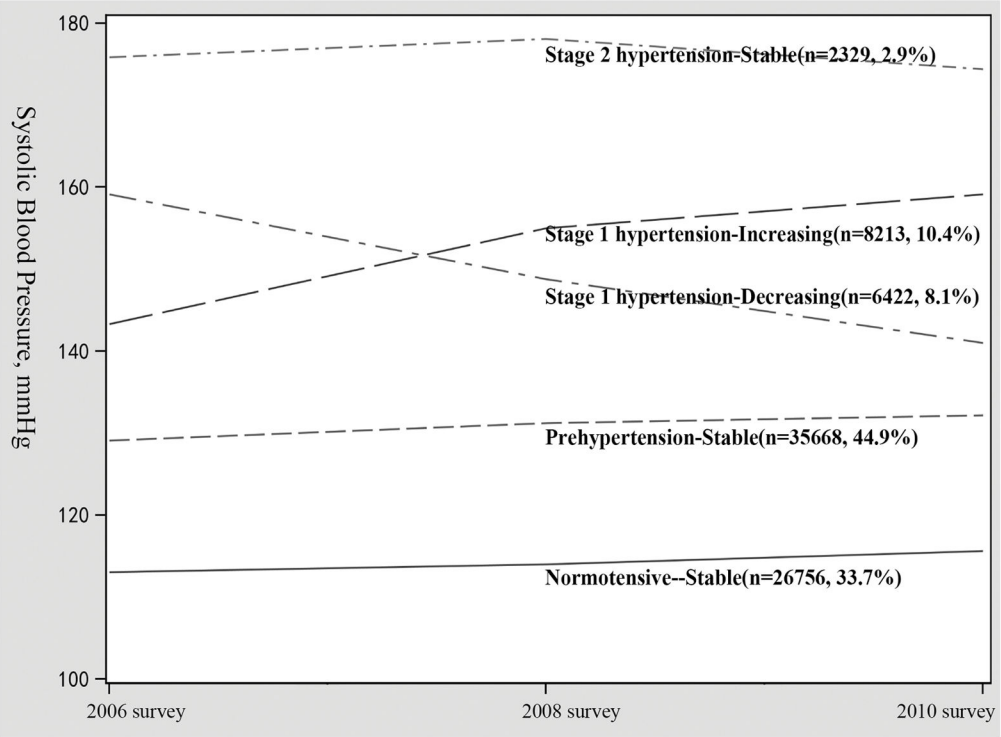

Figure 1.
Systolic blood pressure trajectory patterns during 2006 to 2010

Table 1

Basic characteristics according to 5 subgroups with different SBP trajectory patterns in 79,385 participants of the Kailuan study

Items	Normotensive-stable	Prehypertension-stable	Stage 1 hypertension-increasing	Stage 1 hypertension-decreasing	Stage 2 hypertension-stable
N (%)	26740(33.7)	35674(44.9)	8215(10.4)	6422(8.1)	2334(2.9)
Age, year	44.4	50.7	56.9	55.7	58.8
Women, %	33.2	16.3	15.9	16.3	13.5
Current smoking, %	32.2	36.1	32.6	30.8	35.3
Current alcohol intaking, %	38.2	43.1	42.3	37.8	41.9
Physical activity 3+ times/week, %	10.6	14.4	19.2	19.1	22.9
Salt intake, ≥10 gram/day, %	9.8	10.5	11.0	10.8	12.6
Illiteracy or elementary school, %	4.8	8.6	14.2	12.3	18.7
Average income, <500¥/month, %	26.8	28.9	29.2	28.2	34.4
Use of antihypertensive agent, %	1.1	7.5	21.5	25.1	37.2
Use of lipid-lowering agents, %	0.33	0.76	1.34	0.97	1.24
Use of hypoglycemic agents, %	1.00	1.95	3.48	3.35	3.43
BMI*, Kg/m^2	23.8	25.4	26.1	26.1	26.3
Hs-CRP*, †, mg/L	1.13	1.14	1.43	1.36	1.58
TG*, mmol/L	1.44	1.75	1.83	1.85	1.81
TC*, mmol/L	4.81	5.03	5.17	5.10	5.19
HDL-C*, mmol/L	1.54	1.53	1.54	1.54	1.55
LDL-C*, mmol/L	2.42	2.55	2.62	2.58	2.67
DBP*, mmHg	75	85	93	93	102
PP*, mmHg	37	47	60	59	75
FBG*, mmol/L	5.15	5.47	5.76	5.75	5.84
eGFR*, mL/min/$1.73m^2$	90.4	84.9	80.4	77.7	76.0

*Average levels based on three measurement in 2006, 2008, and 2010

†Geometric mean

Abbreviations: TC, Total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Hs-CRP, high sensitive C-reactive protein; BMI, body mass index; DBP, diastolic blood pressure; PP, pulse pressure; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate.

Table 2

Adjusted Hazard Ratios and 95% confidence intervals for risks of cerebral infarction and intracerebral hemorrhage, according to the 5 subgroups of different SBP trajectory patterns in 79,388 participants of Kailuan study

Stroke type	Normotensive-stable	Prehypertension- stable	Stage 1 hypertension-increasing	Stage 1 hypertension-decreasing	Stage 2 hypertension-stable
Cerebral infarction					
Case # (person year)	102(101326)	421(133672)	236(29786)	170(23633)	105(8278)
Age and sex-adjusted	1.00	2.36(1.90 to 2.94)	4.79(3.77 to 6.10)	4.57(3.55 to 5.89)	7.15(5.39 to 9.48)
Full-adjusted model *	1.00	1.99(1.60 to 2.49)	3.61(2.81 to 4.63)	3.45(2.65 to 4.49)	5.07(3.77 to 6.82)
Further adjusted for SBP in 2006 *	1.00	1.64(1.26 to 2.14)	2.78(2.03 to 3.81)	2.56(1.79 to 3.65)	3.77(2.57 to 5.51)
Further adjusted for SBP in 2010 *	1.00	1.88(1.39 to 2.53)	2.87(1.98 to 4.17)	3.11(2.19 to 4.41)	3.80(2.49 to 5.80)
Excluding 13280 participants who used antihypertensive during 2006–2010 *	1.00	2.00(1.57 to 2.54)	3.70(2.78 to 4.92)	3.54(2.59 to 4.85)	4.96(3.29 to 7.47)
Intracerebral hemorrhage					
Case # (person year)	14(101452)	66(134311)	54(30109)	31(23878)	22(8420)
Age and sex-adjusted	1.00	2.96(1.65 to 5.30)	9.54(5.18 to 17.6)	6.85(3.57 to 13.1)	13.3(6.63 to 26.7)
Full-adjusted model *	1.00	3.11(1.72 to 5.64)	9.66(5.11 to 18.3)	6.79(3.44 to 13.4)	12.4(5.95 to 26.0)
Further adjusted for SBP in 2006 *	1.00	3.39(1.69 to 6.80)	10.8(4.89 to 23.8)	8.20(3.33 to 20.2)	15.0(5.85 to 38.5)
Further adjusted for SBP in 2010 *	1.00	3.21(1.39 to 7.41)	7.24(2.69 to 19.5)	5.97(2.30 to 15.0)	9.82(3.32 to 29.1)
Excluding 13280 participants who used antihypertensive during 2006–2010 *	1.00	2.44(1.29 to 4.62)	8.40(4.13 to 17.1)	8.15(3.84 to 17.3)	13.0 (5.19 to 32.7)

* Adjusted for age(y), sex, smoking (current, past or never), alcohol intake (never, past, light, moderate or heavy), education (illiteracy or elementary school, middle school, or college/university), physical activity (never, sometimes or active), average monthly income of each family member (<500, 500 to 2999 or≥3000¥), salt intake (≥10, 6 to 9 or <6 gram/day), use of hypoglycemic, antihypertensive, lipid-lowering agents and aspirin (yes/no for each), average body mass index (≥30, 25 to 29.9, or <25 Kg/m^2) and estimated glomerular filtration rate(quintile) during 2006 to 2010, and average serum concentrations of triglycerides(quintile), high-density lipoprotein cholesterol(quintile), total cholesterol(quintile), fasting blood glucose(quintile), and high sensitive C-reactive protein (<1, 1 to 3, or≥3mg/ml) during 2006–2010.