Role of blood pressure on stroke-related mortality: a 45-year follow-up study in China

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Abstract

Background: Hypertension is associated with stroke-related mortality. However, the long-term association of blood pressure (BP) and the risk of stroke-related mortality and the influence path of BP on stroke-related death remain unknown. The current study aimed to estimate the long-term causal associations between BP and stroke-related mortality and the potential mediating and moderated mediating model of the associations.

Methods: This is a 45-year follow-up cohort study and a total of 1696 subjects were enrolled in 1976 and 1081 participants died by the latest follow-up in 2020. COX proportional hazard model was used to explore the associations of stroke-related death with baseline systolic blood pressure (SBP)/diastolic blood pressure (DBP) categories and BP changes from 1976 to 1994. The mediating and moderated mediating effects were performed to detect the possible influencing path from BP to stroke-related deaths. E value was calculated in the sensitivity analysis.

Results: Among 1696 participants, the average age was 44.38 ± 6.10 years, and 1124 were men (66.3%). After a 45-year follow-up, a total of 201 (11.9%) stroke-related deaths occurred. After the adjustment, the COX proportional hazard model showed that among the participants with SBP $\geq$ 160 mmHg or DBP $\geq$ 100 mmHg in 1976, the risk of stroke-related death increased by 217.5% (hazard ratio [HR] = 3.175, 95% confidence interval [CI]: 2.297–4.388), and the adjusted HRs were higher in male participants. Among the participants with hypertension in 1976 and 1994, the risk of stroke-related death increased by 110.4% (HR = 2.104, 95% CI: 1.632–2.713), and the adjusted HRs of the BP changes were higher in male participants. Body mass index (BMI) significantly mediated the association of SBP and stroke-related deaths and this mediating effect was moderated by gender.

Conclusions: In a 45-year follow-up, high BP and persistent hypertension are associated with stroke-related death, and these associations were even more pronounced in male participants. The paths of association are mediated by BMI and moderated by gender.

Keywords: Blood pressure; Stroke; Mortality; Mediation; Cohort study

Introduction

The status of hypertension in Chinese adults was the higher prevalence and lower rate of awareness, treatment, and control according to China Hypertension Survey (2012–2015).[1] Hypertension is associated with morbidity, progression, and mortality of cardiovascular disease,[2-4] especially stroke-related death.[5] High systolic blood pressure (SBP) ranked first for the number of deaths accounting for 2.54 million, and ranked second for the

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percentage of disability adjusted life years, namely the lost total health life years from onset hypertension to death in China.[6] Therefore, higher blood pressure (BP), as the strongest causal and high exposure factor, is the leading attributable risk factor for stroke-related death worldwide.[7,8] Nevertheless, the long-term observational research on the associations between BP and BP changes, and stroke-related deaths and the paths of associations are still rare. Most cohort studies were not followed long enough. A cohort study with long enough follow-up in a fixed population did not only observe the long-term association of BP level and death but also explore the influence path under the premise of causal order, and avoid the causal inversion bias. The present study performed a 45-year prospective cohort study to estimate the long-term influence of baseline BP and changes of BP on stroke-related deaths and explore the possible influencing paths.

Methods

Ethics approval

The cohort was approved by the Ethics Committee of the People's Liberation Army General Hospital, China (EC0411-2001). All participants provided their written informed consent.

Subjects

The data in the current study were originated from the Xi'an Machinery Factory cohort study including all employees aged ≥35 years. The information of physical and biochemical examination was collected in the hospital of machinery factory and the teaching hospital of the Fourth Military Medical University, which has been previously reported.[9,10] Form the baseline survey in 1976, the latest follow-up was 2020 with a 3-year follow-up interval. The information of demographics, physiological index, and lifestyle factors were collected through face-to-face interviews by trained staff in 1976 and 1994. The cause of death was recorded in the follow-up every 4 years. In the baseline survey wave, a total of 1842 persons were recruited. After excluding those who lost to follow-up and lacked baseline information, a total of 1696 subjects were enrolled. A total of 169 participants died from stroke-related by the latest follow-up in December 2020.

Exposure

BP was measured twice at 10-min intervals by nurses using a stethoscope and a mercury-stand sphygmomanometer, and the average value served as the BP value. Participants with an SBP < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg were defined as normal BP, while those with SBP ≥140 mmHg and/or DBP ≥90 mmHg were defined as hypertension.[11] To better understand the results, SBP/DBP was grouped into < 130 mmHg/ < 80 mmHg, 130 to 139 mmHg/80 to 89 mmHg, 130 to 139 mmHg/80 to 89 mmHg, and ≥160 mmHg/≥100 mmHg at the baseline. Changes in BP categories from 1976 to 1994 were defined as normal BP → normal BP, normal BP → hypertension, hypertension → normal BP, and hypertension → hypertension.[11]

Covariables

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Total cholesterol (TC) and triglyceride were detected in the medical insurance designated hospital. Self-reported information of demographic characteristics (education, occupation, and marital status), family history of the disease, and lifestyle factors (smoking and drinking) were collected according to the investigation.

Determination of the cause of death

The medical insurance designated hospitals of all participants were fixed, and the pension payment needs to be reported to the local Ministry of Personnel, therefore, the follow-up of death was 100% complete. The determination of the cause of deaths was checked according to ICD-10 (I64.X04) and ICD-11 (8B11, 8B20) by two doctors in the medical insurance hospital every 3 years. The endpoints of this study were stroke-related deaths.

Statistical analysis

Differences among gender and BP groups were performed using Student's *t* and chi-squared test according to the type of variables. The incidence density of mortality was calculated. COX proportional hazard model was used to explore the hazard ratios (HRs) and 95% confidence intervals (CIs) for death in associations with baseline SBP/DBP categories and 19-year changes of BP. Schoenfeld residual trend test was used to test the proportional hazard assumption in the associations of BP categories in 1976/BP change in 1994 and stroke-related death, respectively. The results show that the independent variables (BP/BP change) and the two models meet the preconditions of proportional risk ($P > 0.05$). Models were stratified by gender, and continuous variables such as age, BMI, TC, and categorical variables such as marital status, education, occupation, smoking, drinking, and diabetes were adjusted. While comparing HRs from BP categories or BP changes, the floating absolute risk was used to estimate the HRs and 95% CI.[12] The Cox–Stuart test was used to estimate the trend of the adjusted HRs and 95% CI. The associations between BP and deaths in such a long term were not a simple direct influence, and the exploration of possible paths of associations should not be given up. Therefore, the possible mediations and moderations were performed using the analytic methods.[13] The mediation models explore the independent variable affect the dependent variable in what way or by what variable. In this study, the independent variable (BP in 1976) can exert an indirect effect on the dependent variable (stroke-related deaths in 2020) through an intermediary variable (BMI in 1994). The moderation model explores the different influences of independent variables on the dependent variables in different situations or populations. All mediation and moderated mediation analyses were performed by scripts of PROCESS of SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0. IBM, Armonk, NY, USA).[14] The simple mediating model was tested by PROCESS model 4, and the moderated mediating model by PROCESS model

Table 1: Characteristics of 1696 participants with different baseline BP in 1976.

Characteristics	Total	SBP/DBP categories, mmHg <130/<80 (n = 513)	130–139/80–89 (n = 566)	140–159/90–99 (n = 365)	≥160/≥100 (n = 252)	P values	P for trend
Age (years)	44.38 ± 6.10	43.74 ± 5.29	43.15 ± 5.12	44.7 ± 6.18	47.96 ± 7.90	<0.001	<0.001
TC (mmol/L)	4.63 ± 0.91	4.6 ± 0.89	4.52 ± 0.86	4.68 ± 0.91	4.87 ± 1.00	<0.001	<0.001
TG (mmol/L)	1.14 ± 0.47	1.12 ± 0.45	1.1 ± 0.44	1.18 ± 0.47	1.2 ± 0.57	0.023	0.013
Weight (kg)	63.35 ± 8.09	61.34 ± 7.76	64.33 ± 8.23	63.82 ± 7.46	64.56 ± 8.58	<0.001	<0.001
Height (cm)	169.11 ± 7.56	167.41 ± 7.87	170.46 ± 7.14	169.04 ± 7.39	169.64 ± 7.46	<0.001	<0.001
BMI (kg/m^2)	22.13 ± 2.29	21.87 ± 2.33	22.1 ± 2.19	22.32 ± 2.13	22.42 ± 2.58	0.004	<0.001
Education (years)						0.003	0.133
0–6	590 (34.8)	189 (36.8)	162 (28.6)	127 (34.8)	112 (44.4)		
7–9	620 (36.6)	179 (34.9)	223 (39.4)	141 (38.6)	77 (30.6)		
10–12	297 (17.5)	87 (17)	118 (20.8)	58 (15.9)	34 (13.5)		
≥13	189 (11.1)	58 (11.3)	63 (11.1)	39 (10.7)	29 (11.5)		
Marital status						0.778	0.841
Married	1504 (88.7)	459 (89.5)	499 (88.2)	320 (87.7)	226 (89.7)		
Single/divorced/widowed	192 (11.3)	54 (10.5)	67 (11.8)	45 (12.3)	26 (10.3)		
Occupation						0.696	0.466
Technicians	210 (12.4)	65 (12.7)	74 (13.1)	42 (11.5)	29 (11.5)		
Senior officials and managers	494 (29.1)	149 (29)	173 (30.6)	95 (26)	77 (30.6)		
Workers	992 (58.5)	299 (58.3)	319 (56.4)	228 (62.5)	146 (57.9)		
Smoking						<0.001	0.072
Yes	706 (41.6)	177 (34.5)	277 (48.9)	141 (38.6)	111 (44)		
No	990 (58.4)	336 (65.5)	289 (51.1)	224 (61.4)	141 (56)		
Drinking						0.016	0.004
Yes	328 (19.3)	76 (14.8)	115 (20.3)	81 (22.2)	56 (22.2)		
No	1368 (80.7)	437 (85.2)	451 (79.7)	284 (77.8)	196 (77.8)		
Hypertension history						<0.001	<0.001
Yes	354 (20.9)	1 (0.2)	3 (0.5)	121 (33.2)	229 (90.9)		
No	1342 (79.1)	512 (99.8)	563 (99.5)	244 (66.8)	23 (9.1)		
Diabetes history						0.054	0.097
Yes	178 (10.5)	52 (10.1)	46 (8.1)	49 (13.4)	31 (12.3)		
No	1518 (89.5)	461 (89.9)	520 (91.9)	316 (86.6)	221 (87.7)		
Coronary heart disease history						<0.001	<0.001
Yes	319 (18.8)	70 (13.6)	91 (16.1)	85 (23.3)	73 (29)		
No	1377 (81.2)	443 (86.4)	475 (83.9)	280 (76.7)	179 (71)		

Data are presented as mean ± standard deviation or n(%). BMI: Body mass index; BP: Blood pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride.

5.[15] All mediating and moderated mediating models were based on a 5000 sample bootstrapping set.

E values were reported in the sensitivity analysis, which is related to the potential subject to unmeasured confounding.[16] All analyses were performed using SPSS 24.0, STATA 15.0 (Stata Corp., College Station, TX, US), and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA).

Results

Basic characteristics of 1696 participants in 1976

Among 1696 participants, the average age was 44.38 ± 6.10 years, and 1124 were men (66.3%). No significant statistical differences in SBP and DBP were found between male and female participants. A total of 617 participants were identified with hypertension (36.4%) in 1976, with an average age of 46.04 ± 7.11 years, with 64.8% men. The levels of average age, TC, and BMI were elevated with the increasing BP level ($P_{trend} < 0.05$) [Table 1 and Supplementary Table 1, http://links.lww.com/CM9/A900].

Stroke-related deaths according to the baseline BP

After a 45-year follow-up, a total of 201 stroke-related deaths occurred. The stroke-related mortality in 45 years was 11.9% (95% CI: 10.3–13.4%), and the incidence density was 0.26 per 100 person-years. The incidence density of stroke-related mortality was significantly higher in the participants with hypertension than those without hypertension and higher in male than female participants [Table 2].

The associations between BP and stroke-related mortality

The COX proportional hazard model showed that, after adjusting for age, sex, BMI, marital status, education,

Table 2: Stroke-related mortality according to the baseline hypertension ($N = 1696$).

Parameters	With hypertension		Total
	Yes	No	
Total			
Incident cases/total	102/617	99/1079	201/1696
Incidence (%)	16.5 (13.6–19.5)	9.2 (7.5–10.9)	11.9 (10.3–13.4)
Total person-years	27,765	48,555	76,320
Incidence rate (per 100 person-years)	0.37 (0.30–0.44)	0.20 (0.16–0.24)	0.26 (0.23–0.30)
Male			
Incident cases/total	76/400	69/724	145/1124
Incidence (%)	19.0 (15.1–22.9)	9.5 (7.4–11.7)	12.9 (10.9–14.9)
Total person-years	18,000	32,580	50,580
Incidence rate (per 100 person-years)	0.42 (0.33–0.52)	0.21 (0.16–0.26)	0.29 (0.24–0.33)
Female			
Incident cases/total	26/217	30/355	56/572
Incidence (%)	12.0 (7.6–16.3)	8.5 (5.5–11.4)	9.8 (7.3–12.2)
Total person-years	9765	15,975	25,740
Incidence rate (per 100 person-years)	0.27 (0.16–0.37)	0.19 (0.12–0.25)	0.22 (0.16–0.27)

Data are presented as *n/N*, or *n* (range).

Table 3: HRs of stroke-related death associated with BP categories from 1976 to 2020.

SBP/DBP categories (mm Hg)	*N* of events	Adjusted HR (95% CI)	*P* for trend	*E* values (confidence interval)
Total			<0.001	
<130/< 80	42	1.000 (0.731–1.360)		–
130–139/80–89	57	1.226 (0.927–1.621)		–
140–159/90–99	37	1.251 (0.895–1.748)		–
≥160/≥100	65	3.258 (2.353–4.510)		5.97 (3.90)
Male			<0.001	
<130/< 80	20	1.000 (0.634–1.577)		–
130–139/80–89	49	1.698 (1.258–2.290)		2.79 (1.88)
140–159/90–99	28	1.872 (1.268–2.764)		3.15 (2.23)
≥160/≥100	48	4.984 (3.381–7.346)		9.44 (6.33)
Female			0.046	
<130/< 80	22	1.000 (0.650–1.538)		–
130–139/80–89	8	0.706 (0.345–1.443)		–
140–159/90–99	9	0.722 (0.375–1.391)		–
≥160/≥100	17	2.103 (1.130–3.914)		3.63 (2.88)

Adjusting for age, sex, BMI, marital status, education, occupation, smoking, drinking, diabetes, and TC. BMI: Body mass index; BP: Blood pressure; CI: Confidence interval; DBP: Diastolic blood pressure; HRs: Hazard ratios; SBP: Systolic blood pressure; TC: Total cholesterol.

occupation, smoking, drinking, diabetes, TC, among the participants with SBP ≥160 mmHg or DBP ≥100 mmHg in 1976, the risk of stroke-related death increased by 225.8% (HR = 3.258, 95% CI: 2.353–4.510). In these associations, the risks of stroke-related death were even more pronounced in male participants [Table 3].

Changes in BP levels and subsequent risk of stroke-related mortality

During a 45-year follow-up from 1976 to 2020, 201 stroke-related deaths were recorded, and 169 stroke-related deaths were recorded from 1994 to 2020. After adjusting for age, sex, BMI, marital status, education, occupation, smoking, drinking, diabetes, and TC, changes in BP groups from 1976 to 1994 were associated with stroke-related mortality. Compared with the normal BP → normal BP group, the adjusted HR was 2.104 (95% CI: 1.632–2.713) for the hypertension → hypertension group and the adjusted HRs were 2.415 (95% CI: 1.801–3.239) and 1.895 (95% CI: 1.109–3.239) in male and female participants, respectively [Table 4].

Sensitivity analysis

E value was calculated in the sensitivity analysis, and the *E* values were higher than the HR values. Most *E* values >2 indicated that considerable unmeasured significant confounding factors could be needed to negate the existing HRs, which implied the current associations tended to be more stable [Tables 3 and 4]. Results were consistent in the sensitivity analysis after excluding the participants with

Table 4: HRs of stroke-related death associated with changes of BP categories from 1994 to 2020.

SBP/DBP categories (from 1976 to 1994)	*N* of events	Adjusted HR (95% CI)	*P* for trend	*E* values (Confidence interval)
Total			0.003	3.63 (2.31)
Normal BP → Normal BP	88	1.000 (0.809–1.237)		–
Normal BP → Hypertension	7	1.871 (0.888–3.939)		–
Hypertension → Normal BP	7	0.735 (0.350–1.546)		–
Hypertension → Hypertension	67	2.104 (1.632–2.713)		–
Male			0.002	4.26 (2.94)
Normal BP → Normal BP	62	1.000 (0.775–1.290)		–
Normal BP → Hypertension	4	1.569 (0.583–4.223)		–
Hypertension → Normal BP	5	0.805 (0.335–1.937)		–
Hypertension → Hypertension	49	2.415 (1.801–3.239)		–
Female			0.317	3.20 (2.33)
Normal BP → Normal BP	26	1.000 (0.686–1.457)		–
Normal BP → Hypertension	3	2.172 (0.641–7.363)		–
Hypertension → Normal BP	2	0.531 (0.129–2.191)		–
Hypertension → Hypertension	18	1.895 (1.109–3.239)		–

Adjusting for age, sex, BMI, marital status, education, occupation, smoking, drinking, diabetes, and TC.BMI: Body mass index; BP: Blood pressure; CI: Confidence interval; DBP: Diastolic blood pressure; HRs: Hazard ratios; SBP: Systolic blood pressure; TC: Total cholesterol.

Table 5: The mediating effect of BMI in 1994 between SBP in 1976 and stroke-related deaths in 2020.

Paths	Coefficient	95% CI	*P* values
SBP (1976) → BMI (1994)	0.0282	0.0207–0.0356	<0.0001
BMI (1994) → Stroke-related deaths (2020)	0.0650	0.0068–0.1232	0.0287
SBP (1976) → Stroke-related deaths (2020)	0.0161	0.0080–0.0242	0.0001
SBP (1976) → BMI (1994) → Stroke-related deaths (2020)	0.0018	0.0001–0.0038	0.0010

Adjusting for age, sex, BMI, marital status, education, occupation, smoking, drinking, diabetes, and TC. BMI: Body mass index; CI: Confidence interval; SBP: Systolic blood pressure; TC: Total cholesterol.

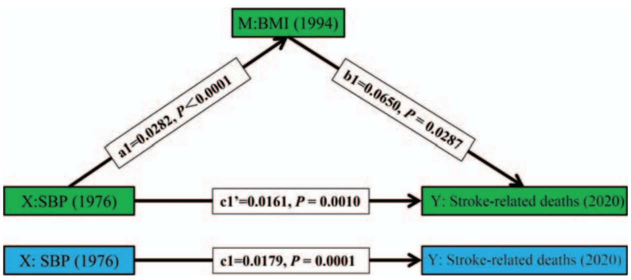

Figure 1: The flow of mediating effect of BMI in 1994 between SBP in 1976 and stroke-related deaths in 2020. The mediating effect accounted for 10.1%. BMI: Body mass index; SBP: Systolic blood pressure. a1: the effect size of SBP on BMI; b1: the effect size of BMI on stroke-related deaths; c1': the direct effect size of SBP on stroke-related deaths; c1: the total effect size of SBP on stroke-related deaths.

Table 6: The moderated mediation analysis of BMI in 1994 between SBP in 1976 and stroke-related deaths in 2020.

Paths	Coefficient	95% CI	*P* value
SBP (1976) → BMI (1994)	0.0286	0.0211–0.0360	<0.0001
BMI (1994) → Stroke-related deaths (2020)	0.0659	0.0076–0.1243	0.0268
SBP (1976) → Stroke-related deaths (2020)	0.0308	0.0071–0.0544	0.0108
SBP (1976) → BMI (1994) → Stroke-related deaths (2020)	0.0019	0.0001–0.0043	0.0005
Moderation factor: Gender			
Male	0.0200	0.0100–0.0300	0.0001
Female	0.0093	−0.0041–0.0226	0.1749

Adjusting for age, sex, BMI, marital status, education, occupation, smoking, drinking, diabetes, and TC. BMI: Body mass index; CI: Confidence interval; SBP: Systolic blood pressure; TC: Total cholesterol.

cardiovascular diseases at baseline [Supplementary Tables 2 and 3, http://links.lww.com/CM9/A900].

The mediation and moderated mediation analysis

We examined, adjusting for the potential confounding factors above, whether BMI in 1994 mediated the influence of BP in 1976 (SBP and DBP) on stroke-related deaths in 2020, respectively. The mediation analysis showed that BMI in 1994, as a statistically significant mediator, partially mediated the effect of SBP in 1976 on stroke-related deaths in 2020, and the mediating effect accounted for 10.1% of the total effect [Table 5 and Figure 1].

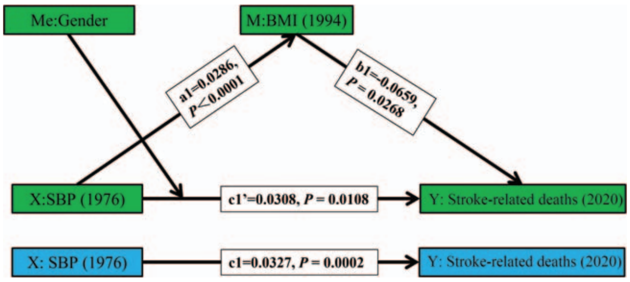

Figure 2: The flow of conditional process analysis (mediation and moderation) of BMI in 1994 between SBP in 1976 and stroke-related deaths in 2020. The mediating effect accounted for 5.8%. BMI: Body mass index; SBP: Systolic blood pressure. a1: the effect size of SBP on BMI; b1: the effect size of BMI on stroke-related deaths; c1': the direct effect size of SBP on stroke-related deaths; c1: the total effect size of SBP on stroke-related deaths.

The moderated mediation analysis showed that the direct effect from SBP to stroke-related death of the mediation model above was moderated by gender, which indicated the effect of SBP on stroke-related death was moderated by male participants. With the moderating effect, the mediating effect accounted for 5.81% of the total effect [Table 6 and Figure 2].

Discussion

The results of our study have shown the long-term positive associations between BP, BP changes, and stroke-related deaths outcomes, highlighting the complexity of the influencing models of the associations. The association of BP and stroke-related death was mediated by BMI and moderated by gender, respectively.

The average SBP and DBP levels were 125.6 ± 20.6 mmHg and 82.3 ± 18.2 mmHg in 1976, and average value in 1994 were 127.7 ± 18.2 mmHg and 83.3 ± 10.5 mmHg. In 1976, China was at the early stage of reform and opening and in the lag period of economic development, and in 1994, China entered a period of rapid economic development. The average BP level increased slightly. This increasing trend was consistent with prior studies.[1,17,18] The prevalence of hypertension has been gradually increasing with age growth and different periods.

High BP level exposure is an independent risk factor of incidence, progression, and mortality of stroke. Whether this causal relationship would be more closely with the increment of exposure duration of high BP was unclear. Studies on this association were limited to the insufficient follow-up time, which would not avoid the inversion of cause and effect. Most observational studies were focused on the morbidity, progression, and mortality cardiovascular disease, which is due to the long-term association of BP and death and insufficient follow-up time.[2,19]

In this study, the 19-year changes in BP were recorded, and the relationship between changes in BP and stroke-related deaths was explored. The changes in BP may be due to lifestyle changes, drug intervention, and other factors. The results have shown that long-term hypertension was associated with stroke-related death to varying degrees, while the associations did not exist in the population with no significant increase in BP. It can be speculated that effective control of BP level may reverse or reduce the risk of stroke-related death. Studies also support the point that these relationships have been reported that the drop in BP from antihypertensive medications provided greater vascular benefits.[20,21]

The results of mediating test suggested that BMI mediated the influence of SBP on stroke-related death, which meant the higher the SBP level, the higher the BMI, and the latter was related with more likely suffering from stroke-related deaths. The results of moderated mediating effect suggested in male participants, BMI mediated this association. At present, no similar study had been found in these models.[22]

This study has some limitations. The results that emerged from the Xi'an machinery factory cohort study may not be able to be generalized to other populations. Second, the results of the baseline survey of family disease histories were self-reported, and recall bias would be difficult to avoid. Third, the information of antihypertensive drugs for cardiovascular disease that might influence BP level was missing, which might provide underestimated the harmful associations of BP and death outcomes.

To conclude, the current study demonstrated that high BP and changes of increased BP indicators were associated with stroke-related death, and the mediating and moderated mediating effects significantly affected these associations. This indicates that the association of high BP indicators and stroke-related death is long-term and multipath progress, which would further verify the necessity of control of hypertension.

Conflicts of interest

None.

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