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Longitudinal change in blood pressure is associated with cardiovascular disease mortality in a Chinese cohort

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Abstract

Background—A number of studies have demonstrated a J-shaped curve between blood pressure and all-cause mortality, but few studies have used longitudinal change in blood pressure to study mortality in the Chinese population.

Methods—We performed a 30-year follow-up study to examine the association between blood pressure (at baseline and longitudinal change) and risk of mortality in the Linxian General Population Trial Cohort. At baseline, a total of 29,584 healthy adults were enrolled in the Linxian General Population Trial in 1985 and followed through the end of 2014. The final analysis was restricted to 29,439 participants(55% women) after exclusion of outliers. We also examined the potential effects of BP trajectory patterns during the period of 1985-1999 on sequent risk of mortality. Adjusted Cox proportional hazards models were used to estimate hazard ratios(HRs) and 95% confidence intervals(95%CIs).

Results—Compared to participants with normal blood pressure, patients with prehypertension, stage 1, stage 2, or stage 3 hypertension had an increased risk of all-cause mortality, with HRs of 1.09(1.05-1.14), 1.34(1.28-1.40), 1.69(1.60-1.79) and 2.14(2.01-2.28), respectively. Relative to

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Competing interests None declared.

Data sharing statement Enquiries can be directed to the corresponding author.

stable BP of normotension, having a rise in BP from normotension to hypertension or from prehypertension to hypertension both conferred an increased risk of total and cardiovascular disease and stroke mortality (Total: HRs=1.22(1.12-1.34) and 1.36(1.23-1.51); Cardiovascular disease: HRs=1.42(1.17-1.73) and 1.55(1.24-1.93); Stroke: HRs=2.29(1.88-2.80) and 2.61(2.11-3.24), respectively).

Conclusions—These findings emphasize that development of incident hypertension in middle age could increase the risk of total, cardiovascular disease, and stroke mortality, and suggest that current blood pressure targets could be revised.

Keywords

Blood pressure; Blood pressure trajectories; Mortality; the Linxian General Population Trial Cohort

INTRODUCTION

The relationship between blood pressure (BP) and mortality has been of interest to epidemiologists and health professionals for several decades. Hypertension is a major risk factor for adverse clinical outcomes including cardiovascular disease, stroke and death [1–3]. Evidence from previous studies has suggested the associations between systolic or diastolic BP and risk of mortality [4–10]. Their results indicated a J-shaped [4, 5] or U-shaped curve[6] phenomenon for the BP-mortality relationship. In addition, BP trajectories may have further impact on mortality. A recent study in Chinese normotensive diabetic people showed that low BP or a decline in BP was associated with an increased risk of all-cause mortality[11], and Tielemans et al[12] also demonstrated that BP trajectories were strong predictors of all-cause mortality. Although previous studies have examined the association between blood pressure and risk of mortality, most studies have been conducted in Western populations and the findings remain unclear.

The Linxian General Population Trial prospectively collected data on clinical outcomes such as cardiovascular disease, cancer, and other diseases. Herein, we reported the results of blood pressure and risk of total, cardiovascular disease, stroke, and cancer mortality from a prospective study of over 30-year follow-up in the Linxian General Population Trial cohort in China. Moreover, we examined the potential effects of BP trajectory patterns during the period of 1985-1999 on sequent risk of mortality.

METHODS

Study population

Detailed information on the Linxian General Population Trial has been described previously[13]. Briefly, the General Population Trial enrolled individuals from the general population of four communes in northern Linxian. Individuals were eligible if they were between 40 and 69 years, lived in one of the four communes, and provided written informed consent. A total of 29,584 healthy adults were randomized and received one of eight daily vitamin/mineral supplement combinations according to a one-half replicate of a 2^4 fractional

factorial design for 5.25 years, beginning in March 1986. Individuals who had cancer, or debilitating diseases were excluded.

In a primary analysis, we excluded participants (N=145) with an extremely low or high BP (those lower or higher than the mean BP ± 3 standard deviations), and a total of 29,439 individuals were included in the final analysis (13,125 men and 16,314 women). In a second analysis, we included individuals who had at least two measurements of BP during1985-1999 (n=10,015; 4,266 men and 5,749 women) to examine the association between BP trajectory patterns and risk of total, cardiovascular disease, stroke and cancer mortality. This study was approved by the institute Review Board of US National Institutes of Health and the Chinese Academy of Medical Science, and all participants gave informed consent for the use of their data.

Data collection

Baseline characteristics data of our study population were obtained using a standard questionnaire. All participants underwent a physical examination in local village hospitals, as well as a questionnaire administered by trained study personnel and research technicians following a standardized protocol that included quality control measures. All participants had their weight and height measured by trained staff. Body weight and height were measured while subjects were not wearing shoes. Body mass index (BMI) was then calculated as weight in kilograms divided by height in meters squared (kg/m^2). According to the WHO/National Heart, Lung, and Blood Institute criteria, subjects were categorized as underweight (BMI<18.5 kg/m^2), normal (18.5 $kg/m^2 \leq$ BMI < 25.0 kg/m^2), overweight (25.0 $kg/m^2 \leq$ BMI < 30.0 kg/m^2) and obesity (BMI ≥ 30.0 kg/m^2), respectively[14]. We obtained demographic and lifestyle data through the questionnaire, including age at baseline, gender, smoking status, alcoholic beverage drinking status, family history of having any cancer, and any medication intake. Smoking was defined as regular cigarette or pipe use for at least six months(including ever or current smokers), and alcohol use was defined as any alcohol consumption in the past 12 months(including ever or current alcohol drinkers). Family history of having any cancer was considered positive if a cancer was reported in at least one first-degree relative. Medication intake was defined as using any drug regularly. In addition, we also collected information on previous chronic disease including cardiovascular disease, stroke, cirrhosis, and diabetes mellitus.

Blood pressure

All subjects had their BP measured in a seated position after resting for 5 minutes using a mercury sphygmomanometer. SBP and DBP were measured as the first and fifth Korotkoff sounds, respectively. BP was measured 3 times about 5 minutes apart, and the mean of these 3 measures was used for analysis. BP was measured again in 1999 since the baseline, and the same procedure for BP measurement was used. In our study, we used two different metrics for BP to evaluate the association between BP and risk of mortality: (1) the baseline BP; and (2) the BP trajectory patterns during 1985-1999. In the second analysis, we excluded patients who had BP of 140/90 mmHg or higher at baseline.

Mortality follow-up

During the trial period (1986-1991), village doctors visited all participants monthly, and all endpoints were confirmed by an International Endpoints Review Committee consisting of American and Chinese experts in cytology, pathology, surgery, and radiology. During the post-trial follow-up periods (after 1991), village doctors continued to visit all participants monthly, and new cancer cases and all causes of death were verified by a panel of Chinese experts. Diagnostic materials used in these expert reviews included case records, pathology and cytology slides, biochemical results, X rays, ultrasound, endoscopy and surgery reports. Primary causes of death were identified by the International Classification of Disease, Tenth Revision (ICD-10): cardiovascular disease (I00-I25, I28-I59), stroke (I60-I69) and cancer (C00-C97).

Statistical analysis

All subjects were divided into 6 groups, including hypotension [SBP < 90 mm Hg and(or) DBP < 60 mmHg], normotension [90 mm Hg ≤ SBP <120 mm Hg and 60 mm Hg ≤DBP< 80 mmHg], prehypertension [120 mm Hg ≤ SBP<140 mmHg and(or) 80 mm Hg ≤ DBP< 90 mmHg], stage 1 hypertension [140 mm Hg ≤ SBP < 160 mm Hg and(or) 90 mm Hg ≤ DBP <100 mm Hg], stage 2 hypertension [160 mm Hg ≤SBP < 180 mm Hg and(or) 100 mm Hg ≤ DBP < 110 mm Hg] and stage 3 hypertension [SBP ≥ 180 mm Hg and(or) DBP≥ 110 mm Hg][15]. Participants were censored at the last known follow-up date, death, or December 31, 2014, whichever came first. In the BP trajectory analysis, the initial date for follow-up was defined from the most recent examination (1999). We tested the differences in six categories using nonparametric Kruskal-Wallis Test for continuous variables and Chi Square Test for categorical variables.

We used Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for examining the association between BP and risk of total, cardiovascular disease, cancer mortality. We also tested the assumption of proportional risk for the Cox models by using cross-product terms (time×blood pressure) and using Kaplan-Meier curves. Normotensive subjects were defined as a reference category in the analysis. Moreover, our analyses were adjusted for the following covariates: age at baseline (continuous variable), sex(men or women), BMI (continuous variable), education level (never or one to five years or primary school or tertiary high school or higher education or others), tobacco smoking (yes or no), alcohol drinking(yes or no),family history of cancer (yes or no), commune (Rencun, Yaocun, Hengshui or Donggang), pulse rate (continuous variable) and any medication intake (yes or no). Subgroup analyses were performed to examine whether the association varied by sex (men or women), age at baseline (<60 or ≥60), smoking (yes or no), alcohol drinking (yes or no), BMI (<18.5, 18.5-25.0 or ≥25.0) and follow-up duration (<3 or ≥3). Sensitivity analyses were also performed by excluding smokers or drinkers or patients who had preexisting chronic disease or had extreme BMIs or were followed up less than three years. To address the possibility of residual confounding by measured variables, we first created a propensity score that reflected associations of blood pressure with the other variables in a logistic regression model and then further adjusted for the propensity score in the Cox regression model. We also evaluated possible non-linear associations by comparing the fit of continuous models with and without BP quadratic terms using a

likelihood ratio test, and graphed the association using the BP linear and quadratic terms relative to the 12.5th percentile (sFigure 1 and sFigure 2). In a second analysis, we examined the associations between BP trajectory patterns and risk of total, cardiovascular disease, stroke and cancer mortality. Subjects with a stable BP of <120/80 mmHg were regarded as a reference group. BP trajectory patterns were stable in normotension, normotension to prehypertension, normotension to hypertension, prehypertension to normotension, stable in prehypertension and prehypertension to hypertension.

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). All tests were two sided and P<0.05 was considered statistically significant.

RESULTS

A total of 29,439 participants were included in the final analysis. During 582,925 person-years (mean: 19.8 person-years) of follow-up, 19,403 deaths (including 4,692 from cardiovascular disease, 6,247 from stroke and 5,731 from cancer) were identified. Of the eligible subjects, more than half (55.4%) were women. Mean age at baseline was 51.9 years. According to the 1999 WHO/ISH guidelines, nearly 19% of participants were regarded as normotension, with 402 hypotensive patients (1%), 11,031 prehypertensive patients (38%) and 1,2401 hypertensive patients (42%). Hypertensive patients were more likely to be older and to have lower education, were less commonly smokers and drinkers. Overweight/obesity was more prevalent among hypertensive patients (Table 1).

Table 2 shows HRs and 95% CIs for the associations between BP and risk of total, cardiovascular disease, stroke and cancer mortality. Compared with normotensive subjects, prehypertensive and hypertensive patients had an increased risk of all-cause mortality, with HRs of 1.09(1.05-1.14) (prehypertension), 1.34(1.28-1.40) (stage 1 hypertension), 1.69(1.60-1.79) (stage 2 hypertension) and 2.14(2.01-2.28) (stage 3 hypertension), respectively. We also examined cause-specific mortality, and observed stronger associations for stroke mortality (Table 2, sTable 1). No significant associations were observed for cancer mortality.

Subgroup analyses showed that the relationship between BP and all-cause mortality did not materially alter by age at baseline, sex, BMI, smoking, alcohol drinking and duration of follow-up (Table 3). Results appeared similar across subgroups by age at baseline, sex, smoking status and BMI. Significant associations were observed for hypotension and risk of total mortality among nondrinkers and individuals who had no family history of cancer, and the HRs were 1.20 (1.02-1.40) and 1.25 (1.06-1.47), respectively. When stratified by duration of follow-up, stronger associations were observed for prehypertension/hypertension and all-cause mortality in the follow-up of three years and more.

Exclusion of smokers, drinkers, subjects who had preexisting chronic disease or were followed up less than three years or had extreme BMIs (<18.5 or >40 kg/m^2) did not materially alter our findings. A similar relationship was also observed among non-smokers, non-drinkers, participants who had no preexisting chronic disease or had extreme BMIs, or

subjects with the follow-up of three years and more. Further adjustment for propensity score for BP in Cox models did not alter our findings (Figure 1, sTable 2).

Figure 2 summaries the associations between BP trajectories and risk of total, cardiovascular disease, stroke and cancer mortality. Compared with persons who had a stable BP of <120/80mmHg, the adjusted HR for all-cause mortality was 1.22 (95% CI: 1.12, 1.34) for increase BP from <120/80 mmHg to ≥140/90 mmHg, and 1.36 (95% CI: 1.23, 1.51) for increase BP from 120-139/80-89 mmHg to≥v140/90 mmHg. No significant associations were observed between other BP trajectory patterns and total mortality. For cause-specific mortality, stronger associations were observed for cardiovascular disease and stroke mortality among subjects with development of incident hypertension, and we also found significant associations for cardiovascular disease mortality among subjects with stable prehypertension (HR=1.75, 95% CI: 1.29, 2.39) or from normotension to prehypertension (HR=1.32, 95% CI: 1.04, 1.68). No associations were observed in any BP trajectory pattern for cancer mortality. Subgroup analyses indicated slightly stronger associations between development of incident hypertension and total mortality in women (sTable 3).

DISCUSSION

The present study examines the association between BP (at baseline and trajectory patterns) and risk of mortality in the Linxian General Population Trial Cohort. Overall, significant associations were observed for BP and risk of total, cardiovascular disease and stroke mortality. When compared with normotensive subjects, prehypertensive and hypertensive persons had a higher risk of all-cause, cardiovascular disease and stroke mortality. No associations were observed for cancer mortality. Sensitivity analyses by excluding smokers, alcohol drinkers, subjects who had extreme BMIs or previous chronic disease or followed up the first three years did not alter our findings. A BP trajectory analysis showed that individuals with increased BP from <120/80 mmHg or 120-139/80-89 mmHg to ≥ 140/90 mmHg had an increased risk of total, cardiovascular disease and stroke mortality.

Our findings of positive associations for BP>120/80 mm Hg and risk of cardiovascular mortality were comparable to a previous study in Korea. A study of 1,235,246 individuals from the Korean Cancer Prevention Study has indicated J-curve associations between SBP and vascular mortality [16]. The Systolic Blood Pressure Intervention Trial (SPRINT)[17] Research Group concluded that among patients at high risk for cardiovascular events but without diabetes mellitus, lowering systolic blood pressure to a target goal of less than 120 mmHg rather than <140 mmHg could reduce 25% risk of major cardiovascular events and 43% of cardiovascular mortality. Several trials such as the Systolic Hypertension in the Elderly Program Trial[18] and the Systolic Hypertension in Europe trial[19] suggested the benefits of systolic blood pressure targets below 150 mm Hg, and the Eighth Joint National Committee (JNC-8) recommended systolic BP goal of lower than 150 mmHg in the elderly[20]. This recommendation was primarily derived from two large randomized clinical trials. Some limitations of these studies should be considered, including the short median follow-up duration (only 2 years). Another limitation is that both studies were conducted in Japan where there is low incidence of coronary heart disease compared with other parts of the world and the result might extrapolate to the other regions. However, it is still

controversial for the current blood pressure targets [21]. Adequate control of elevated BP could help prevent cardiovascular events and mortality, and new concepts in hypertension management have been reported in several recent studies[22–24]. As expected, in our study, we observed no associations between hypertension and risk of cancer mortality. A number of epidemiological studies have indicated either positive or no associations for elevated BP and cancer mortality[25–27]. A pooled analysis of 7 cohorts from Norway, Austria and Sweden has suggested a higher risk of cancer death with elevated BP[27]. However, there is little support for hypertension and cancer incidence or mortality in a cohort study of Japanese-American men in Hawaii[25]. The discrepancy in results between these studies may be explained by chance, unknown confounders, different study designs, differences in the study populations, or the specific cancer types that dominate different populations.

One use of a single measurement of BP at baseline might contribute to an underestimated relative risk with regression dilution bias[28]. BP trajectory patterns over time may have greater power in predicting risk of total and cardiovascular mortality. Limited studies in China have examined the potential effect of longitudinal change in BP. In our study, we included participants with at least two measurements of BP to examine the potential effect of BP trajectories. We observed development of hypertension conferred a higher risk of total, cardiovascular disease and stroke mortality. However, one possible interpretation is the relationship of elevated BP with vascular aging[29], and thus caused cardiovascular events and then results in death from these diseases.

Some caution is necessary in the interpretation of our results. In fact, smoking or alcohol drinking is associated with BP and an increased risk of mortality[30] and there is also a strong association between smoking and drinking habits. This suggested that smoking and drinking can distort the relationship between BP and risk of mortality. Moreover, a potential limitation for observational studies is the possibility for residual or uncontrolled confounding. We further excluded smokers and drinkers in our study to address this potential bias and results did not change. We further adjusted for a propensity score that reflected associations of blood pressure with the other variables, which did not alter our results.

Our study had several important strengths, including its prospective design, large sample size, longitudinal patterns of change in BP during follow-up period, a homogeneous ethnic group, and over 30 years follow-up. Our study also had several limitations. Firstly, although we had information on tobacco smoking, alcohol drinking, education and BMI, we lacked information on other potential confounders, such as physical activity and total energy intake. As in other observational studies, our results could potentially reflect the confounding effect by physical activity or other lifestyle factors. Furthermore, in our study, we lacked information on antihypertensive drug use over time, which could affect our results. Secondly, some of our significant findings may also have been due to the number of tests that were not included in the pre-specified hypotheses. Thirdly, although persons with self-reported cancer, debilitating diseases (severe kidney and liver disease) were excluded from our study, we collected data of cardiovascular disease, stroke, cirrhosis, and diabetes mellitus at baseline and results did not alter when exclusion of these chronic diseases. Finally, our subjects were composed of rural Chinese adults, and had fewer women smokers

and drinkers than the general Chinese population, which may affect the generalizability of our results to other Chinese populations.

In summary, in this large prospective study, positive associations were observed for BP and risk of total, cardiovascular disease and stroke mortality. Prehypertension and hypertension were associated with an increased risk of total, cardiovascular disease and stroke mortality. BP trajectory patterns from normotensive levels to 140/90 mmHg or higher were associated with increased risk of total, cardiovascular disease and stroke mortality. Further studies are needed to confirm these findings in other ethnic/regional populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Lewington S, Lacey B, Clarke R, et al. The Burden of Hypertension and Associated Risk for Cardiovascular Mortality in China. JAMA Intern Med. 2016; 176:524–532. [PubMed: 26975032]
2. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2224–2260. [PubMed: 23245609]
3. Yano Y, Stamler J, Garside DB, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascularmortality: the Chicago Heart Association Detection Project in Industry study. J Am Coll Cardiol. 2015; 65:327–335. [PubMed: 25634830]
4. Shih CJ, Chen YT, Ou SM, et al. Observed Blood Pressure and Mortality Among People Aged 65 Years and Older: A Community-Based Cohort Study. J Am Med Dir Assoc. 2016; 17:654–662. [PubMed: 27209272]
5. Pastor-Barriuso R, Banegas JR, Damián J, et al. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. Ann Intern Med. 2003; 139:731–739. [PubMed: 14597457]
6. Okumiya K, Matsubayashi K, Wada T, et al. A U-shaped association between home systolic blood pressure and four-year mortality in community-dwelling older men. J Am Geriatr Soc. 1999; 47:1415–1421. [PubMed: 10591234]
7. Odden MC, McClure LA, Sawaya BP, et al. Achieved Blood Pressure and Outcomes in the Secondary Prevention of Small Subcortical Strokes Trial. Hypertension. 2016; 67:63–69. [PubMed: 26553236]
8. Koh AS, Talaei M, Pan A, et al. Systolic blood pressure and cardiovascular mortality in middle-aged and elderly adults - The Singapore Chinese Health Study. Int J Cardiol. 2016; 219:404–409. [PubMed: 27362831]
9. Takashima N, Ohkubo T, Miura K, et al. Long-term risk of BP values above normal for cardiovascular mortality: a 24-year observation of Japanese aged 30 to 92 years. J Hypertens. 2012; 30:2299–2306. [PubMed: 23079682]

10. Hirai Y, Geleijnse JM, Adachi H, et al. Systolic blood pressure predicts cardiovascular mortality in a farming but not in a fishing community. -A 40-year follow up of the Japanese cohorts of the seven countries study. Circ J. 2011; 75:1890–1896. [PubMed: 21673459]
11. Wu Z, Jin C, Vaidya A, et al. Longitudinal Patterns of Blood Pressure, Incident Cardiovascular Events, and All-Cause Mortality in Normotensive Diabetic People. Hypertension. 2016; 68:71–77. [PubMed: 27217407]
12. Tielemans SM, Geleijnse JM, Menotti A, et al. Ten-year blood pressure trajectories, cardiovascular mortality, and life years lost in 2 extinction cohorts: the Minnesota Business and Professional Men Study and the Zutphen Study. J Am Heart Assoc. 2015; 4:e1378.
13. Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China-supplementation with specific vitamin mineral combinations, cancerincidence, and disease-specific mortality in the general-population. J Natl Cancer Inst. 1993; 85:1483–1492. [PubMed: 8360931]
14. National Institutes of Health. Clinical guidelineson the identification, evaluation, and treatment of overweightand obesity in adults: the evidence report. Obes Res. 1998; 6:51S–209S. [PubMed: 9813653]
15. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289:2560–2572. [PubMed: 12748199]
16. Yi SW, Mok Y, Ohrr H, et al. Low Systolic Blood Pressure and Vascular Mortality Among More Than 1 Million Korean Adults. Circulation. 2016; 133:2381–2390. [PubMed: 27143683]
17. SPRINT Research Group. Wright JT Jr, Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015; 373:2103–2116. [PubMed: 26551272]
18. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991; 265:3255–3264. [PubMed: 2046107]
19. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350:757–764. [PubMed: 9297994]
20. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014; 311:507–520. [PubMed: 24352797]
21. Messerli FH, Bangalore S. Introduction: Controversies in Hypertension. Prog Cardiovasc Dis. 2016; 59:207–208. [PubMed: 27978963]
22. Milani RV, Lavie CJ, Wilt JK, Bober RM, Ventura HO. New Concepts in Hypertension Management: A Population-Based Perspective. Prog Cardiovasc Dis. 2016; 59:289–294. [PubMed: 27693860]
23. Kario K. Evidence and Perspectives on the 24-hour Management of Hypertension: Hemodynamic Biomarker-Initiated ‘Anticipation Medicine’ for Zero Cardiovascular Event. Prog Cardiovasc Dis. 2016; 59:262–281. [PubMed: 27080202]
24. Milani RV, Bober RM, Lavie CJ. The Role of Technology in Chronic Disease Care. Prog Cardiovasc Dis. 2016; 58:579–83. [PubMed: 26772623]
25. Grove JS, Nomura A, Severson RK, et al. The association of blood-pressure with cancer incidence in a prospective-study. Am J Epidemiol. 1991; 134:942–947. [PubMed: 1951291]
26. Chow WH, Gridley G, Fraumeni JF Jr, et al. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med. 2000; 343:1305–1311. [PubMed: 11058675]
27. Stocks T, Van Hemelrijck M, Manjer J, et al. Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. Hypertension. 2012; 59:802–810. [PubMed: 22353615]
28. Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. Am J Epidemiol. 1999; 150:341–353. [PubMed: 10453810]
29. Nilsson PM, Lurbe E, Laurent S. The early life origins of vascular ageing and cardiovascular risk: the EVA syndrome. J Hypertens. 2008; 26:1049–1057. [PubMed: 18475139]

30. Wakabayashi I. Modification of the association of alcohol drinking with blood pressure by cigarette smoking. Blood Press. 2008; 17:87–93. [PubMed: 18568697]

• Key messages

What is already known on this subject?

A J-shaped association between systolic or diastolic blood pressure and all-cause mortality has been shown in previous studies.

What might this study add?

In the present study, significant associations were observed for BP at baseline and risk of total, cardiovascular disease and stroke mortality. Individuals with increased BP from <120/80 mmHg or 120-139/80-89 mmHg to ≥ 140/90 mmHg had an increased risk of total, cardiovascular disease and stroke mortality.

How might this impact on clinical practice?

Adequate control of elevated BP could help prevent cardiovascular events and mortality, and our findings suggest that current blood pressure targets could be reconsidered.

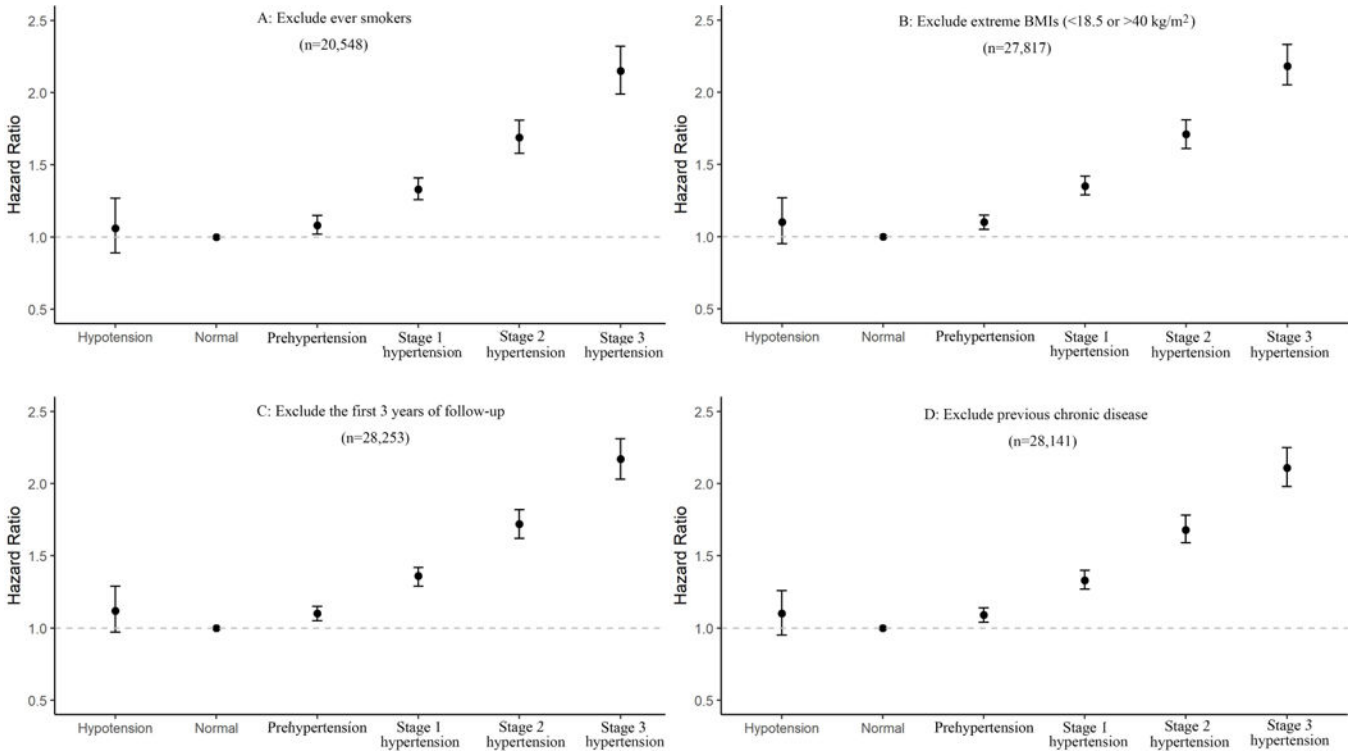

Figure 1. Hazard ratios (HRs) for all-cause mortality according to clinical classification of blood pressure among subjects who were non-smokers, had BMIs of 18.5-40 kg/m^2, were followed up three years and more, and had no preexisting chronic disease

(A: Exclude ever smokers; B: Exclude extreme BMIs (<18.5 or >40 kg/m^2); C: Exclude the first 3 years of follow-up; D: Exclude previous chronic disease)

Hypotension: subjects with blood pressure (BP)<90/60 mmHg; Normotension: subjects with BP of 90-119/60-79 mmHg; Prehypertension: subjects with BP of 120-139/80-89 mmHg; Stage 1 hypertension: subjects with BP of 140-159/90-99 mmHg; Stage 2 hypertension: subjects with BP of 160-179/100-109 mmHg; Stage 3 hypertension: subjects with BP≥180/110 mmHg. HRs and 95% CIs were calculated by adjustment for age at baseline, sex, BMI, commune, education level, tobacco smoking, alcohol drinking, family history of cancer, pulse rate and any drug intake. 95% CIs: 95% confidence intervals.

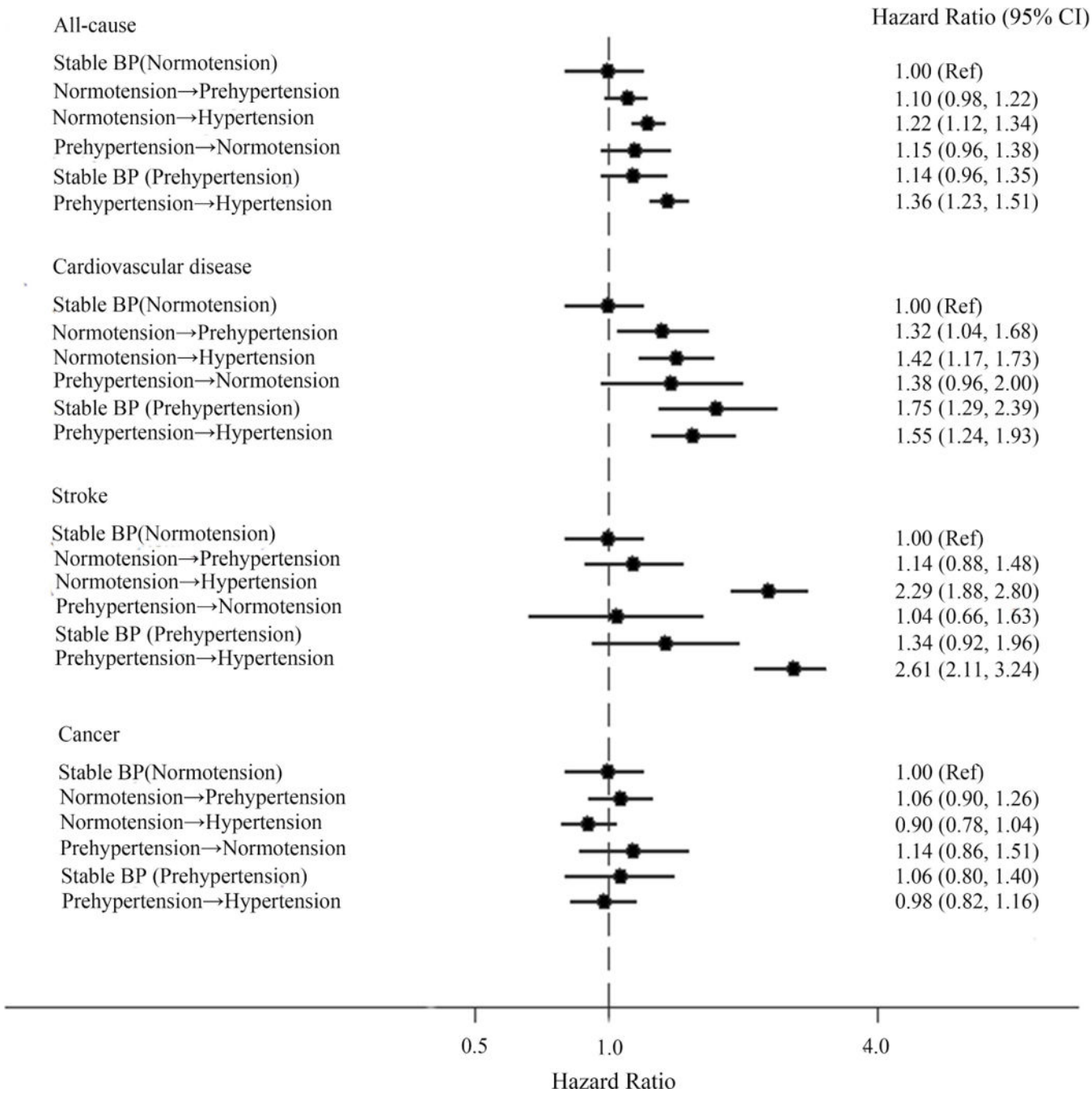

Figure 2. Hazard ratios (HRs) for risk of mortality due to all-cause, cardiovascular disease, stroke and cancer according to BP trajectory patterns

Normotension: subjects with blood pressure (BP) of less than 120/80 mmHg; Prehypertension: subjects with BP of 120-139/80-89 mmHg; Hypertension: subjects with BP≥140/90mmHg. HRs and 95% CIs were calculated by adjustment for age at baseline, sex, BMI, commune, education level, tobacco smoking, alcohol drinking, family history of cancer, pulse rate and any drug intake. 95% CIs: 95% confidence intervals.

Table 1

Baseline characteristics according to different clinical categories of blood pressure in the Linxian General Population Trial Cohort

	Hypotension (n=402)	**Normotension (n=5605)**	**Prehypertension (n=11031)**	**Stage 1 hypertension (n=7485)**	**Stage 2 hypertension (n=2956)**	**Stage 3 hypertension (n=1960)**	***P* value**
Women (n, %)	187(46.5)	3049(54.4)	5887(53.4)	4141(55.3)	1762(59.6)	1288(65.7)	<0.01
Age(yr; median, IQR)	48.0(42.0,55.0)	47.0(41.0,54.0)	49.0(43.0,56.0)	54.0(48.0,60.0)	58.0(51.0,63.0)	60.0(54.0,64.0)	<0.01
Pulse rate(bpm; median, IQR)	72.0(65.0,76.0)	72.0(66.0,75.0)	72.0(68.0,76.0)	72.0(68.0,78.0)	72.0(68.0,78.0)	73.0(70.0,80.0)	
Follow-up(yr; median, IQR)	26.6(14.3, 29.7)	27.9(16.4, 29.7)	24.6(14.5, 29.7)	18.7(10.7, 29.6)	14.2(8.0, 22.9)	10.9(6.1, 17.9)	<0.01
SBP(mmHg; median, IQR)	90.0(80.0, 90.0)	104.0(100.0, 110.0)	120.0(120.0, 130.0)	140.0(130.0, 140.0)	160.0(150.0, 165.0)	180.0(180.0,195.0)	-
DBP(mmHg; median, IQR)	50.0(50.0, 55.0)	70.0(60.0,70.0)	80.0(80.0, 80.0)	90.0(80.0, 90.0)	100.0(90.0, 100.0)	110.0(100.0,110.0)	-
BMI (kg/m^2; median, IQR)	21.1(19.8,22.4)	21.4(20.1,22.8)	21.8(20.4,23.2)	21.8(20.4,23.5)	22.0(20.5,23.9)	22.2(20.7,24.2)	
BMI (kg/m^2; n, %)							<0.01
Underweight	32(8.0)	377(6.7)	556(5.0)	431(5.8)	140(4.7)	81(4.1)	
Normal	349(86.8)	4887(87.2)	9408(85.3)	6165(82.4)	2360(79.8)	1529(78.0)	
Overweight	21(5.2)	329(5.9)	1023(9.3)	844(11.3)	431(14.6)	321(16.4)	
Obesity	0(0.0)	12(0.2)	44(0.4)	45(0.6)	25(0.9)	29(1.5)	
Education* (n, %)							<0.01
Never	123(30.6)	1726(30.8)	3898(35.3)	3373(45.1)	1540(52.1)	1144(58.4)	
Less than 5 years	136(33.8)	1905(34.0)	3542(32.1)	2330(31.1)	807(27.3)	464(23.7)	
Primary school	56(13.9)	806(14.4)	1385(12.6)	639(8.5)	163(5.5)	99(5.1)	
Tertiary high school or higher education	52(12.9)	753(13.4)	1253(11.4)	471(6.3)	136(4.6)	40(2.0)	
Others	35(8.7)	415(7.4)	953(8.6)	672(9.0)	310(10.5)	213(10.9)	
Smoking(n, %)							<0.01
No	258(64.2)	3782(67.5)	7561(68.5)	5235(69.9)	2180(73.8)	1532(78.2)	
Yes	144(35.8)	1823(32.5)	3470(31.5)	2250(30.1)	776(26.3)	428(21.8)	
Drinking(n, %)							<0.01
No	286(71.1)	4123(73.6)	8234(74.6)	5802(77.5)	2410(81.5)	1671(85.3)	
Yes	116(28.9)	1482(26.4)	2797(25.4)	1683(22.5)	546(18.5)	289(14.7)	
Family history of cancer(n,%)							0.01
No	261(64.9)	3630(64.8)	7200(65.3)	4883 (65.2)	1988 (67.3)	1346 (68.7)	
Yes	141 (35.1)	1975 (35.2)	3831 (34.7)	2602 (34.8)	968 (32.7)	614 (31.3)	

	Hypotension (n=402)	Normotension (n=5605)	Prehypertension (n=11031)	Stage 1 hypertension (n=7485)	Stage 2 hypertension (n=2956)	Stage 3 hypertension (n=1960)	*P* value
Commune(n, %)							
Yaocun	191 (47.5)	1962 (35.0)	3682 (33.4)	2228 (29.8)	1086 (36.7)	766(39.1)	<0.01
Rencun	55 (13.7)	950 (17.0)	2438 (22.1)	1788 (23.9)	431 (14.6)	265(13.5)	
Donggang	64 (15.9)	1303 (23.2)	2278 (20.7)	1565 (20.9)	625 (21.1)	409(20.9)	
Hengshui	92 (22.9)	1390 (24.8)	2633 (23.9)	1904 (25.4)	814 (27.5)	520(26.5)	

IQR: Interquartile Range; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Hypotension: SBP < 90 mm Hg and(or) DBP <60 mm Hg; Normotension: 90 mm Hg ≤ SBP<120 mmHg and 60 mm Hg ≤ DBP< 80 mmHg; Prehypertension: 120 mm Hg ≤ SBP<140 mmHg and(or) 80 mm Hg ≤ DBP < 90 mmHg; Stage 1 hypertension: 140 mm Hg ≤ SBP <160 mm Hg and(or) 90 mm Hg ≤ DBP <100 mm Hg; Stage 2 hypertension: 160 mm Hg ≤ SBP < 180 mm Hg and(or) 100 mm Hg ≤ DBP <110 mm Hg; Stage 3 hypertension: SBP ≥180 mm Hg and (or) DBP ≥ 110 mm Hg.

Table 2

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for total and cause-specific mortality, associated with different groups of clinical classification of blood pressure

Causes of death	Hypotension	Normotension (Reference)	Prehypertension	Stage 1 hypertension	Stage 2 hypertension	Stage 3 hypertension
All-cause mortality						
N	402	5605	11031	7485	2956	1960
No. of death cases	223	2840	6429	5568	2537	1806
No. of death cases per 1000 person-year	25.48	22.32	27.12	40.03	55.46	72.22
Age and sex adjusted HR (95% CI)	1.10(0.96-1.27)	1.00	**1.09(1.04-1.14)**	**1.34(1.28-1.40)**	**1.68(1.59-1.77)**	**2.13(2.01-2.27)**
Multivariable HR (95% CI) *	1.11(0.97-1.28)	1.00	**1.09(1.05-1.14)**	**1.34(1.28-1.40)**	**1.69(1.60-1.79)**	**2.14(2.01-2.28)**
Cardiovascular disease						
No. of death cases	49	640	1519	1380	649	455
Age and sex adjusted HR (95% CI)	1.09(0.82-1.46)	1.00	**1.10(1.00-1.21)**	**1.31(1.19-1.44)**	**1.61(1.44-1.80)**	**1.96(1.73-2.22)**
Multivariable HR (95% CI) *	1.12(0.83-1.49)	1.00	**1.11(1.01-1.22)**	**1.31(1.19-1.44)**	**1.66(1.48-1.86)**	**2.04(1.79-2.32)**
Stroke						
No. of death cases	47	566	1703	1963	1031	937
Age and sex adjusted HR (95% CI)	1.18(0.88-1.59)	1.00	**1.47(1.34-1.62)**	**2.47(2.24-2.71)**	**3.66(3.30-4.07)**	**6.15(5.51-6.85)**
Multivariable HR (95% CI) *	1.20(0.89-1.62)	1.00	**1.46(1.33-1.60)**	**2.41(2.19-2.65)**	**3.55(3.20-3.95)**	**5.92(5.30-6.62)**
Cancer						
No. of death cases	93	1130	2232	1487	529	260
Age and sex adjusted HR (95% CI)	1.14(0.92-1.41)	1.00	0.97(0.91-1.05)	0.97(0.90-1.05)	0.96(0.87-1.07)	**0.84(0.73-0.96)**
Multivariable HR (95% CI) *	1.13(0.92-1.40)	1.00	0.98(0.91-1.05)	0.97(0.90-1.05)	0.99(0.89-1.10)	0.87(0.75-1.00)

Hypotension: SBP < 90 mm Hg and (or) DBP < 60 mm Hg; Normotension: 90 mm Hg ≤SBP <120 mm Hg and 60 mm Hg ≤DBP < 80 mmHg; Prehypertension: 120 mm Hg ≤ SBP <140 mmHg and (or) 80 mm Hg ≤ DBP < 90 mmHg; Stage 1 hypertension: 140 mm Hg ≤ SBP < 160 mm Hg and (or) 90 mm Hg ≤DBP < 100 mm Hg; Stage 2 hypertension: 160 mm Hg ≤ SBP < 180 mm Hg and (or) 100 mm Hg ≤ DBP <110 mm Hg; Stage 3 hypertension: SBP ≥ 180 mm Hg and (or) DBP ≥ 110 mm Hg.

*Adjusted for age at baseline, sex, BMI, commune, education level, tobacco smoking, alcohol drinking, family history of cancer, pulse rate and any drug intake.

Table 3

Subgroup analyses of the associations between clinical classification of blood pressure and risk of all-cause mortality

Subgroup	Hypotension	Normotension (Reference)	Prehypertension	Stage 1 hypertension	Stage 2 hypertension	Stage 3 hypertension
Age at baseline *						
<60 years	1.09(0.93-1.27)	1.00	**1.06(1.01-1.12)**	**1.32(1.25-1.39)**	**1.74(1.63-1.87)**	**2.30(2.12-2.50)**
≥60 years	1.24(0.92-1.67)	1.00	**1.19(1.08-1.31)**	**1.37(1.24-1.50)**	**1.66(1.50-1.84)**	**2.08(1.87-2.32)**
Sex#						
Men	1.07(0.90-1.28)	1.00	**1.07(1.00-1.13)**	**1.32(1.24-1.41)**	**1.63(1.50-1.77)**	**2.18(1.98-2.40)**
Women	1.16(0.94-1.43)	1.00	**1.12(1.05-1.20)**	**1.36(1.27-1.46)**	**1.75(1.62-1.89)**	**2.16(1.98-2.35)**
Smoking&						
No	1.06(0.89-1.27)	1.00	**1.08(1.02-1.15)**	**1.33(1.26-1.41)**	**1.69(1.58-1.81)**	**2.15(1.99-2.32)**
Yes	1.19(0.96-1.47)	1.00	**1.10(1.03-1.19)**	**1.34(1.24-1.45)**	**1.69(1.54-1.87)**	**2.17(1.92-2.44)**
Drinking†						
No	**1.20(1.02-1.40)**	1.00	**1.10(1.04-1.16)**	**1.35(1.28-1.43)**	**1.67(1.56-1.78)**	**2.13(1.98-2.28)**
Yes	0.91(0.69-1.20)	1.00	1.08(0.99-1.18)	**1.29(1.18-1.42)**	**1.81(1.60-2.04)**	**2.20(1.90-2.56)**
BMI *						
<18.5	1.25(0.81-1.94)	1.00	1.08(0.92-1.27)	1.15(0.97-1.36)	**1.46(1.16-1.82)**	**1.61(1.23-2.11)**
18.5 to <25	1.11(0.96-1.29)	1.00	**1.10(1.05-1.15)**	**1.35(1.28-1.42)**	**1.68(1.58-1.78)**	**2.20(2.05-2.36)**
≥25	0.90(0.46-1.76)	1.00	1.10(0.92-1.31)	**1.39(1.17-1.66)**	**1.98(1.63-2.39)**	**2.22(1.82-2.72)**
Family history of cancer						
No	**1.25(1.06-1.47)**	1.00	**1.14(1.08-1.21)**	**1.39(1.31-1.47)**	**1.75(1.63-1.87)**	**2.26(2.10-2.45)**
Yes	0.90(0.71-1.15)	1.00	1.01(0.94-1.09)	**1.25(1.16-1.35)**	**1.59(1.45-1.75)**	**1.93(1.73-2.15)**
Follow-up period *						
<3 years	0.96(0.52-1.77)	1.00	0.92(0.75-1.12)	1.02(0.83-1.24)	**1.31(1.04-1.64)**	**1.73(1.37-2.18)**
≥3 years	1.12(0.97-1.29)	1.00	**1.10(1.05-1.15)**	**1.36(1.29-1.42)**	**1.72(1.62-1.82)**	**2.17(2.03-2.31)**

Hypotension: SBP <90 mm Hg and (or) DBP<60 mm Hg; Normotension: 90 mm Hg ≤ SBP<120 mmHg and 60 mm Hg ≤DBP< 80 mmHg; Prehypertension: 120 mm Hg ≤SBP<140 mmHg and(or) 80 mm Hg ≤DBP< 90 mmHg; Stage 1 hypertension: 140 mm Hg≤ SBP<160 mm Hg and (or) 90 mm Hg ≤DBP <100 mm Hg; Stage 2 hypertension: 160 mm Hg ≤ SBP < 180 mm Hg and (or) 100 mm Hg ≤ DBP < 110 mm Hg; Stage 3 hypertension: SBP ≥180 mm Hg and (or) DBP ≥ 110 mm Hg.

*Adjusted for age at baseline, sex, BMI, commune, education level, tobacco smoking, alcohol drinking, family history of cancer, pulse rate and any drug intake.

#Adjusted for age at baseline, BMI, commune, education level, tobacco smoking, alcohol drinking, family history of cancer, pulse rate and any drug intake.

[&] Adjusted for age at baseline, sex, BMI, commune, education level, alcohol drinking, family history of cancer, pulse rate and any drug intake.

[†] Adjusted for age at baseline, sex, BMI, commune, education level, tobacco smoking, family history of cancer, pulse rate and any drug intake.