Original Investigation | Cardiology

Association of Lifestyle Factors and Antihypertensive Medication Use With Risk of All-Cause and Cause-Specific Mortality Among Adults With Hypertension in China

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Abstract

IMPORTANCE The joint association of antihypertensive medication use and healthy lifestyle with mortality among individuals with hypertension is unclear.

OBJECTIVE To examine the association of lifestyle factors combined with antihypertensive medication use, as well as changes in lifestyle, with all-cause and cause-specific mortality among individuals with hypertension.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from the Dongfeng-Tongji cohort, a long-term, prospective cohort including employees at a manufacturer in China, with baseline from 2008 to 2010. Participants with hypertension were followed up for a median (IQR) of 7.3 (5.7-10.3) years, ending in 2018. Data were analyzed from February to April 2021.

EXPOSURES Lifestyle factors, including body mass index, smoking status, diet, physical activity, and sleep duration, were coded on a 3-point scale (range, 0-2, with higher score indicating a healthier lifestyle). Lifestyle was evaluated according to the total score of all 5 factors, and categorized into 3 groups: unfavorable (scores 0-4), intermediate (scores 5-7), and favorable (scores 8-10). Antihypertensive medication use was defined as use within the last 2 weeks.

MAIN OUTCOMES AND MEASURES All-cause, cardiovascular, and cancer mortality were identified by linking the cohort database with the health care system through December 31, 2018.

RESULTS A total of 14 392 participants (mean [SD] age, 65.6 [7.4] years; 7277 [50.6%] men and 7115 [49.4%] women) with hypertension were included, and 2015 deaths were documented, including 761 cardiovascular deaths and 525 cancer deaths. Compared with individuals not using antihypertensive medication and with a lifestyle score of 0 to 4, the combination of using antihypertensive medication and having a lifestyle score of 8 to 10 was associated with the lowest risk of all-cause mortality (hazard ratio [HR], 0.32; 95% CI, 0.25-0.42), cardiovascular mortality (HR, 0.33; 95% CI, 0.21-0.53), and cancer mortality (HR, 0.30; 95% CI, 0.19-0.47). In addition, improvement in lifestyle score after hypertension diagnosis was associated with lower risk of all-cause mortality (HR, 0.52; 95% CI, 0.36-0.76) and cardiovascular mortality (HR, 0.53; 95% CI, 0.30-0.94).

CONCLUSIONS AND RELEVANCE These findings suggest that adherence to healthy lifestyle and antihypertensive medication treatment were associated with lower risk of mortality among adults with hypertension. These findings further support that, in addition to antihypertensive medication

(continued)

Key Points

Question Are the combination of antihypertensive medication use and healthy lifestyle, as well as the change in lifestyle, associated with mortality among individuals with hypertension?

Findings In this cohort study of 14 392 individuals with hypertension, adherence to healthy lifestyle and antihypertensive medication treatment was associated with lower risk of all-cause, cardiovascular, and cancer mortality. Improvement in lifestyle after hypertension diagnosis was also associated with significantly lower risk of mortality.

Meaning These findings suggest that in addition to antihypertensive medication use, adopting a healthy lifestyle is associated with benefits in the prevention of premature death among individuals with hypertension.

+ **Supplemental content**

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Abstract (continued)

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Introduction

Hypertension is a major public health concern, affecting 1.13 billion adults worldwide.[1] Despite the considerable advances in antihypertensive medication treatments, the prevalence of hypertension has been increasing over the past 40 years.[2] Elevated blood pressure (BP) is a leading cause of cardiovascular disease (CVD) and mortality[3] and accounts for more than 10 million deaths in 2019.[4] It is paramount to identify effective strategies to prevent or delay the poor prognosis for individuals with hypertension.

Adherence to antihypertensive medication treatment and following a healthy lifestyle are important parts of hypertension self-management.[5] Nonadherence to medication regimen has been reported in 10% to 80% of patients with hypertension, with higher rates in low-income countries and rural areas,[6,7] and is an essential risk factor for nonoptimal BP control and cardiovascular events.[8,9] Maintaining a healthy lifestyle can improve vascular health, prevent or delay the onset of hypertension, and is associated with lower cardiovascular risk.[10-12] Moreover, it is suggested that lifestyle modification may be more important than medication treatment for mild hypertension.[13] However, the evidence regarding the long-term health outcomes associated with the combination of antihypertensive medication use and healthy lifestyle among individuals with hypertension is limited. Although epidemiologic studies have suggested that individuals with hypertension who adopted a relatively healthy lifestyle but did not use antihypertensive medications had a lower risk of stroke or heart failure, compared with those who used antihypertensive medications but did not adhere to a healthy lifestyle,[14,15] no study has examined the joint association of antihypertensive medication use and healthy lifestyle with mortality among individuals with hypertension, to our knowledge. In addition, whether improvement in lifestyle may yield health benefits for individuals with hypertension is unclear.

To fill these knowledge gaps, we aimed to prospectively examine the association of antihypertensive medication use and healthy lifestyle, as well as changes in lifestyle, with risk of all-cause and cause-specific mortality among middle-aged and elderly adults with hypertension in China.

Methods

This cohort study was approved by the Medical Ethics Committee of the School of Public Health, Tongji Medical College, Huazhong University of Science and Technology and Dongfeng General Hospital, Dongfeng Motor Corporation (DMC), Shiyan City, China. All participants provided written informed consent. Our study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Population

The Dongfeng-Tongji (DFTJ) study is an ongoing dynamic cohort that consecutively recruits retired employees of DMC.[16] The DFTJ study was launched in 2008, and 2 follow-up surveys have been completed since. Briefly, 27 009 participants were recruited at baseline from September 2008 to June 2010. Among these, 25 978 individuals (96.2%) were followed up in 2013; meanwhile, 14 120 new retirees were additionally enrolled into the cohort. In 2018, we completed the second follow-up

survey. The detailed timeline is presented in eFigure 1 in the Supplement. Face-to-face interviews, physical examinations, and blood draws were conducted at all surveys.

This study included 17 308 participants with prevalent hypertension, defined as self-reported physician-diagnosed hypertension or use of antihypertensive medication within the last 2 weeks (including 9719 participants from 2008, 3875 participants from 2008-2013, and 3714 participants from 2013). After excluding 1031 participants with cancer at baseline and those with incomplete information on antihypertensive medication use (60 participants) or any components of lifestyle (1825 participants), a total of 14 392 participants with hypertension were included in the final analysis (eFigure 1 in the Supplement).

Assessment of Lifestyle Factors

Lifestyle factors assessed included body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), smoking status, diet, physical activity, and sleep duration. BMI was grouped into 3 categories as reference range (18.5-24.9), overweight (25.0-29.9), and obese or underweight (≥30.0 or <18.5).[17] According to previous literature,[1] underweight was associated with increased mortality rate among older adults at a higher rate even than overweight. Thus, in our analysis, overweight was categorized as intermediate lifestyle, and underweight and obese were grouped into unfavorable lifestyle. In addition, among 14 392 participants included in the current analysis, only 216 (1.5%) were underweight. In a sensitivity analysis, we also used the Asian BMI cutoff (ie, overweight: ≥24.0; obese: ≥28.0). Smoking status was grouped into noncurrent smokers (never smoking or having quit >10 years), former smokers having quit 10 years or less, and current smokers.

Information on the frequency and mean duration of leisure-time physical activity, including walking, jogging, biking, playing ball games, dancing, tai chi, swimming, exercising at the gym, and others, was collected through questionnaire. Metabolic equivalents (METs) were used to define moderate (3 to <6 METs) and vigorous (≥6 METs) activities, such as 3 METs for walking, 4 METs for biking, 4.5 METs for tai chi, 5 METs for dancing or calisthenics, 6 METs for playing ball games or exercising at the gym, and 7.5 METs for jogging and swimming. The optimal level of physical activity was defined as weekly moderate activities for at least 150 minutes or weekly vigorous activities for at least 75 minutes. Intermediate level of physical activity referred to any level of moderate or vigorous activities greater than 0 but not reaching optimal level. Physical inactivity was considered as no moderate or vigorous activities.

Diet was assessed based on 3 food components, including vegetables, fruits, and meat, that were addressed in the 2013 American Heart Association guideline on lifestyle management to reduce cardiovascular risk.[18] Participants were assigned 1 point for each if they consumed vegetables at least twice a day, fruits at least once a day, or meat less than once a day; otherwise, 0 points. Diet quality was graded according to the total score: favorable (3 points), intermediate (2 points), and unfavorable (0-1 point).

According to the J-shaped association between sleep duration and all-cause mortality reported in previous literature,[19] nighttime sleep duration was divided into 3 groups: optimal (6-8 hours/day), intermediate (5-5.9 or 8.1-10 hours/day), and poor (<5 or >10 hours/day).

Definition of Overall Favorable Lifestyle

Overall favorable lifestyle was evaluated based on the aforementioned 5 lifestyle factors, which have been highlighted in recent guidelines in the prevention and treatment of hypertension.[7] We coded 2 points to participants for each low-risk factor: BMI within reference range, noncurrent smoking status, engaging in optimal level of physical activity, favorable diet, and optimal sleep duration. Participants with high-risk factors were coded 0 points, including those who were obese or underweight, current smoking status, physical inactivity, unfavorable diet, and poor sleep duration. The remaining lifestyle factors were assigned 1 point. Overall lifestyle score was the sum of the individual scores of all 5 lifestyle factors, ranging from 0 to 10, with a higher score indicating a

healthier lifestyle. Participants were categorized into 3 groups using the cutoff values of lifestyle score that were most practical and with sufficient statistical power in each category: favorable (8-10 points), intermediate (5-7 points), and unfavorable (0-4 points) lifestyle.

Assessment of Antihypertensive Medication Use and Other Covariates

Use of antihypertensive medication was classified as responding yes to the question *Have you used any antihypertensive medications within the last 2 weeks?* Other covariates, including age, sex, education attainment, drinking status, hypertension duration, self-reported physician-diagnosed diabetes or CVD (including coronary heart disease, myocardial infraction, and stroke), and use of hypoglycemic and lipid-lowering medication, were obtained via questionnaires. Mental stress (available only in the first survey) was defined according to 7 yes or no questions about stress and mental status in the past 1 month, ie, losing interest, feeling tired or low on energy, weight change, sleep disorders, difficult concentrating, thought about death, or feeling worthless. Participants were categorized into 3 groups: with 3 or more symptoms, 1 to 2 symptoms, or no symptoms.

In addition, BP was measured by trained investigators according to standard procedures. Metabolic biomarkers, including fasting glucose, glycated hemoglobin A_{1c}, total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, and creatinine levels, were measured among the participants who provided blood samples at baseline and follow-up surveys. The details are documented elsewhere.[16] Estimated glomerular filtration rate was computed based on the Chronic Kidney Disease Epidemiology Collaboration equation.[20]

Ascertainment of Mortality

Vital status was confirmed by linkage with the health care system of DMC that archived death certificates of all retirees through December 31, 2018. The *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* was used to define cardiovascular deaths (*ICD-10* codes I00-I99) and cancer deaths (*ICD-10* codes C00-C97).

Statistical Analysis

Basic Information

Participants were categorized into 6 groups according to different combinations of antihypertensive medication use (yes or no) and overall lifestyle (unfavorable, intermediate, and favorable). Baseline characteristics were described across groups. Person-years were calculated from the date responding to questionnaires to the date when death occurred or the end of follow-up (December 31, 2018), whichever came first. Missing values of covariates (<4.4%) were imputed with median for continuous variables and missing indicators for categorical variables.

Association of Lifestyle and Antihypertensive Medication Use With Mortality

Cox proportional hazards regression models were used to examine the joint associations of antihypertensive medication use and lifestyle with risk of all-cause, CVD, and cancer mortality, considering participants not using antihypertensive medication and following an unfavorable lifestyle as the reference. In model 1, we adjusted for age (continuous) and sex (male vs female). In model 2, we further adjusted for education attainment (<high school, high school or equivalent, or ≥college), drinking status (current, former, or never drinker), hypertension duration (≤5, >5-10, or >10 years), self-reported physician-diagnosed diabetes or CVD, and uses of hypoglycemic and lipid-lowering medication. In model 3, we additionally adjusted for systolic and diastolic BP, fasting glucose, and HDL cholesterol levels and estimated glomerular filtration rate (all continuous). These covariates were selected based on prior literature.[21,22] The proportional hazard assumption was tested based on Schoenfeld residuals and no violation was found. The generalized linear model was used to investigate the associations of overall lifestyle with blood glucose and lipids at baseline. A restricted cubic spline model with 3 knots (25th, 50th, and 75th) was applied to test dose-response

associations between lifestyle score and mortality among participants with hypertension with and without antihypertensive medication use.

Changes in Lifestyle and Risk of Mortality

To evaluate the association between changes in lifestyle and risk of mortality, we conducted analysis in a subgroup of 6863 participants who completed both baseline and the first follow-up surveys. Changes in lifestyle were assessed from baseline to the first follow-up, and deaths were identified after the first follow-up. Lifestyle score greater than 5 was considered as high; less than 5, low. Participants were categorized into 4 groups: consistently low, high to low, low to high, and consistently high. The covariates adjusted in the multivariable model were obtained in the first follow-up, with the consistently low group as the reference.

Secondary Analysis

Stratified analyses were conducted by age (<65 vs ≥65 years), sex (male vs female), education attainment (<high school, high school, or ≥college), duration of hypertension (≤10 vs >10 years), and history of diabetes (yes vs no). In addition, several sensitivity and secondary analyses were performed. First, analyses were performed separately in participants using antihypertensive medication. Lifestyle score was included in models as categorical and continuous variables. Interaction associations between antihypertensive medication use (yes or no) and lifestyle (favorable, intermediate, or unfavorable) and mortality were tested using the likelihood ratio test by including an additional product term in the model. Second, we evaluated the associations of different components of lifestyle behaviors with all-cause mortality. Third, we also constructed a weighted lifestyle score based on β coefficients of each lifestyle factor in the Cox proportional hazards regression model with all 5 lifestyle factors included. Fourth, to further test the contribution of individual lifestyle factors, we omitted 1 lifestyle factor each time to reconstruct a new 8-point lifestyle score, and participants were categorized into scores 0 to 4, 5 to 6, and 7 to 8. Fifth, we excluded participants diagnosed with CVD before baseline or those died within 2 years of follow-up to minimize the potential reverse causation bias. Sixth, the main analysis was repeated only in participants with complete data. Finally, given the potential confounding of psychological factors in the association of interest,[23] mental stress was further adjusted for in a subset of study population.

Analyses were performed using Stata statistical software, version MP 16.0 (StataCorp) and R version 3.6.1 (R Project for Statistical Computing). Two-tailed P < .05 was considered statistically significant. Data were analyzed from February to April 2021.

Results

Table 1 shows the baseline characteristics of 14 392 participants with hypertension (mean [SD] age, 65.6 [7.4] years; 7277 [50.6%] men and 7115 [49.4%] women). Compared with participants not using antihypertensive medication and following an unfavorable lifestyle, those using antihypertensive medication and adhering to a favorable lifestyle had longer duration of hypertension (>10 years: 74 participants [33.5%] vs 2405 participants [53.7%]), higher prevalence of diabetes (51 participants [21.6%] vs 1285 participants [27.5%]) and CVD (53 participants [22.5%] vs 1550 participants [33.1%]), lower mean (SD) systolic (148 [22] mm Hg vs 142 [20] mm Hg) and diastolic (86 [13] mm Hg vs 81 [12] mm Hg) BP, and were more likely to use hypoglycemic (18 participants [7.6%] vs 807 participants [17.2%]) and lipid-lowing (22 participants [9.3%] vs 1370 participants [29.3%]) medications (Table 1). In addition, higher lifestyle score was associated with lower level of triglyceride and higher level of HDL cholesterol, regardless of antihypertensive medication use. Among patients using antihypertensive medication, higher lifestyle score was also associated with lower levels of fasting glucose and glycated hemoglobin A_{1c} (eTable 1 in the Supplement). There were differences in some characteristics of participants included and excluded from our analyses (eTable 2 in the Supplement).

During a median (IQR) follow-up of 7.3 (5.7-10.3) years, we documented 2015 deaths, including 761 CVD deaths and 525 cancer deaths. Compared with participants not using antihypertensive medication and following an unfavorable lifestyle, those who used antihypertensive medications and had a favorable lifestyle had the lowest risk of all-cause mortality (hazard ratio [HR], 0.32; 95% CI, 0.25-0.42), CVD mortality (HR, 0.33; 95% CI, 0.21-0.53), and cancer mortality (HR, 0.30; 95% CI, 0.19-0.47) (**Table 2**). Furthermore, compared with the reference group, participants without antihypertensive medication treatment but who adopted a favorable lifestyle had lower risks of all-cause mortality (HR, 0.34; 95% CI, 0.25-0.46), CVD mortality (HR, 0.40; 95% CI, 0.24-0.67), and cancer mortality (HR, 0.33; 95% CI, 0.19-0.55); whereas those using antihypertensive medication but following an unfavorable lifestyle had no significant reduction in risk of CVD mortality (HR, 0.71; 95% CI, 0.43-1.17) or cancer mortality (HR, 0.64; 95% CI, 0.38-1.07).

Dose-response analyses showed inverse linear associations between lifestyle score and all-cause, CVD, and cancer mortality, regardless of antihypertensive medication use (**Figure**). Each 1-point increase in lifestyle score was associated with a 17% lower risk of all-cause mortality, 15% lower risk of CVD mortality, and 18% lower risk of cancer mortality for participants not using

Table 1. Baseline Characteristics According to Antihypertensive Medication Use and Lifestyle Score

Characteristic	No. (%)					
	Not using antihypertensive medication			Using antihypertensive medication		
	Score of 0-4	Score of 5-7	Score of 8-10	Score of 0-4	Score of 5-7	Score of 8-10
No.	236	1938	1594	637	5305	4682
Age, mean (SD), y	65.8 (7.3)	65.0 (7.3)	65.0 (7.8)	65.7 (7.4)	65.8 (7.2)	65.7 (7.6)
Sex						
Women	51 (21.6)	794 (41.0)	995 (62.4)	135 (21.2)	2235 (42.1)	2905 (62.0)
Men	185 (78.4)	1144 (59.0)	599 (37.6)	502 (78.8)	3070 (57.9)	1777 (38.0)
Education attainment						
<High school	178 (76.4)	1382 (71.9)	1063 (66.9)	437 (69.0)	3553 (67.4)	2884 (62.0)
High school or equivalent	40 (17.2)	378 (19.7)	397 (25.0)	134 (21.2)	1189 (22.6)	1173 (25.2)
≥College	15 (6.4)	162 (8.4)	129 (8.1)	62 (9.8)	527 (10.0)	597 (12.8)
Alcohol consumption						
Nondrinker	109 (46.2)	1154 (59.7)	1219 (76.5)	292 (45.8)	3434 (64.8)	3798 (81.2)
Current	110 (46.6)	642 (33.2)	307 (19.3)	267 (41.9)	1366 (25.8)	618 (13.2)
Former	17 (7.2)	137 (7.1)	67 (4.2)	78 (12.2)	500 (9.4)	262 (5.6)
Duration of hypertension, y						
≤5	103 (46.6)	1060 (56.9)	933 (60.2)	148 (24.8)	1270 (25.2)	1132 (25.3)
>5-10	44 (19.9)	308 (16.5)	220 (14.2)	135 (22.7)	1119 (22.2)	945 (21.1)
>10	74 (33.5)	495 (26.6)	397 (25.6)	313 (52.5)	2655 (52.6)	2405 (53.7)
Self-reported						
Diabetes	51 (21.6)	501 (25.9)	333 (20.9)	203 (31.9)	1653 (31.2)	1285 (27.5)
CVD	53 (22.5)	432 (22.3)	303 (19.0)	254 (39.9)	1884 (35.5)	1550 (33.1)
Use of hypoglycemic medication	18 (7.6)	181 (9.3)	145 (9.1)	124 (19.5)	1010 (19.0)	807 (17.2)
Use of lipid-lowering medication	22 (9.3)	199 (10.3)	172 (10.8)	199 (31.2)	1638 (30.9)	1370 (29.3)
Blood pressure, mm Hg						
Systolic	148 (22)	149 (20)	150 (21)	140 (20)	142 (20)	142 (20)
Diastolic	86 (13)	86 (12)	85 (12)	82 (12)	82 (12)	81 (12)
Fasting glucose, mean (SD), mg/dL	110.63 (39.28)	112.79 (36.58)	110.09 (29.73)	116.58 (39.28)	114.95 (34.77)	111.89 (32.25)
HDL cholesterol, mean (SD), mg/dL	54.44 (17.76)	55.60 (17.37)	57.53 (15.44)	52.9 (16.99)	53.67 (16.22)	55.98 (16.60)
eGFR, mean (SD), mL/min/1.73 m^2	82.0 (33.9)	81.7 (24.5)	80.0 (23.5)	80.9 (36.4)	78.2 (29.4)	77.5 (24.5)

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; HDL cholesterol to millimoles per liter, multiply by 0.0259.

antihypertensive medication, and a 14% lower risk of all-cause mortality, 14% lower risk of CVD mortality, and 13% lower risk of cancer mortality for those using medication. No significant interactions were found between antihypertensive medication use and lifestyle score (eTable 3 in the Supplement). For different combinations of lifestyle factors, the multivariable-adjusted model found a significant association per 1-point increase in lifestyle score when only BMI, smoking status, and diet were included in lifestyle score (adjusted HR [aHR], 0.92; 95% CI, 0.89-0.95). The risk decreased when physical activity and sleep duration were additionally included in the score (physical activity: aHR, 0.88; 95% CI, 0.85-0.90; sleep duration: aHR, 0.86; 95% CI, 0.83-0.88) (eTable 4 in the Supplement). Furthermore, the inverse associations between lifestyle score and risk of mortality were largely similar when using weighted lifestyle score (eTable 5 in the Supplement) or omitting 1 lifestyle factor each time from the total score (eTable 6 in the Supplement).

Improvement in lifestyle after hypertension diagnosis was also significantly associated with lower risk of all-cause and cause-specific mortality (**Table 3**). Compared with participants with consistently low lifestyle score between baseline and first follow-up survey, participants who improved their lifestyle score (low to high) had decreased risk of all-cause mortality (HR, 0.52; 95% CI, 0.36-0.76), CVD mortality (HR, 0.53; 95% CI, 0.30-0.94), and cancer mortality (0.73; 95% CI, 0.37-1.44), and those having a consistently high lifestyle score also had reduced risk of all-cause mortality (HR, 0.51; 95% CI, 0.39-0.67), CVD mortality (HR, 0.51; 95% CI, 0.34-0.77), and cancer mortality (HR, 0.52; 95% CI, 0.30-0.89).

Consistent results were observed in subgroup analyses stratified by age, sex, education attainment, duration of hypertension, and self-reported diabetes (eFigure 2 in the Supplement). The results were essentially unchanged when excluding participants diagnosed with CVD before baseline (eTable 7 in the Supplement), excluding participants who died within 2 years of follow-up (eTable 8 in the Supplement), or only including participants with complete data (eTable 9 in the Supplement). The results were attenuated with additional adjustment for mental stress (eTable 10 in the

Table 2. All-Cause and Cause-Specific Mortality According to Antihypertensive Medication Use and Lifestyle Score Among Participants With Hypertension

	HR (95% CI)					
	Not using antihypertensive medication, lifestyle score, points			Using antihypertensive medication, lifestyle score, points		
	0-4	5-7	8-10	0-4	5-7	8-10
Person-years, No.	1606	13 764	11 437	4694	41 943	38 142
Participants, No.	236	1938	1594	637	5305	4682
All-cause mortality						
Deaths, No.	63	243	138	163	855	553
Model 1[a]	1 [Reference]	0.49 (0.37-0.64)	0.34 (0.25-0.45)	0.80 (0.60-1.08)	0.48 (0.37-0.62)	0.35 (0.27-0.45)
Model 2[b]	1 [Reference]	0.47 (0.36-0.62)	0.34 (0.25-0.46)	0.70 (0.52-0.93)	0.43 (0.33-0.56)	0.32 (0.25-0.42)
Model 3[c]	1 [Reference]	0.48 (0.36-0.63)	0.34 (0.25-0.46)	0.70 (0.52- 0.94)	0.43 (0.33-0.56)	0.32 (0.25-0.42)
CVD mortality						
Deaths, No.	21	87	56	60	329	208
Model 1[a]	1 [Reference]	0.52 (0.32-0.84)	0.40 (0.24-0.66)	0.83 (0.51-1.37)	0.52 (0.34-0.82)	0.32 (0.25-0.42)
Model 2[b]	1 [Reference]	0.39 (0.23-0.64)	0.39 (0.23-0.64)	0.67 (0.40-1.10)	0.43 (0.28-0.68)	0.31 (0.20-0.49)
Model 3[c]	1 [Reference]	0.51 (0.32-0.83)	0.40 (0.24-0.67)	0.71 (0.43-1.17)	0.46 (0.29-0.72)	0.33 (0.21-0.53)
Cancer mortality						
Deaths, No.	22	60	43	44	206	150
Model 1[a]	1 [Reference]	0.34 (0.21-0.56)	0.30 (0.18-0.50)	0.65 (0.39-1.09)	0.34 (0.22-0.53)	0.28 (0.18-0.44)
Model 2[b]	1 [Reference]	0.35 (0.21-0.57)	0.32 (0.19-0.54)	0.64 (0.38-1.07)	0.35 (0.22-0.54)	0.30 (0.19-0.47)
Model 3[c]	1 [Reference]	0.35 (0.22-0.58)	0.33 (0.19-0.55)	0.64 (0.38-1.07)	0.35 (0.22-0.54)	0.30 (0.19-0.47)

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.

[a] Adjusted for age (continuous), and sex (male vs female).

[b] Further adjusted for education attainment (<high school, high school or equivalent, ≥college), drinking status (never drinker, former drinker, or current drinker), hypertension duration (≤5, >5 to 10, or >10 years), self-reported physician-diagnosed CVD (yes or no) and diabetes (yes or no), and uses of hypoglycemic (yes or no) or lipid-lowering (yes or no) medication.

[c] Further adjusted for systolic blood pressure (continuous), diastolic blood pressure (continuous), fasting glucose (continuous), HDL cholesterol (continuous), and eGFR (continuous).

Supplement). Similar findings were observed when using the Asian BMI cutoff (eTable 11 in the Supplement).

Discussion

Among participants with hypertension in a prospective cohort in China, we found that the combination of using antihypertensive medication and adhering to a favorable lifestyle (weight within reference range, nonsmoking, adequate physical activity, high-quality diet, and optimal sleep duration) was significantly associated with lower risks of mortality. The association was independent of traditional risk factors, including hypertension duration, common comorbidities, use of hypoglycemic and lipid-lowering medication, metabolic biomarkers, and mental stress. In addition, improvement in lifestyle after hypertension diagnosis was also associated with lower risk of subsequent premature death. The stratified and sensitivity analyses demonstrated the robustness of the findings.

Large-scale population-based studies have reported that nonadherence to or discontinuation of antihypertensive medication was associated with higher risks of stroke or myocardial infarction.[8,24,25] However, the adherence to medication treatment decreased over time. An Italian study of 13 303 patients with newly diagnosed hypertension reported that 42.6% of participants stopped any antihypertensive medication within the first year after hypertension diagnosis.[26]

Figure. Dose-Response Association of Lifestyle Score With Mortality According to Hypertension Medication Use
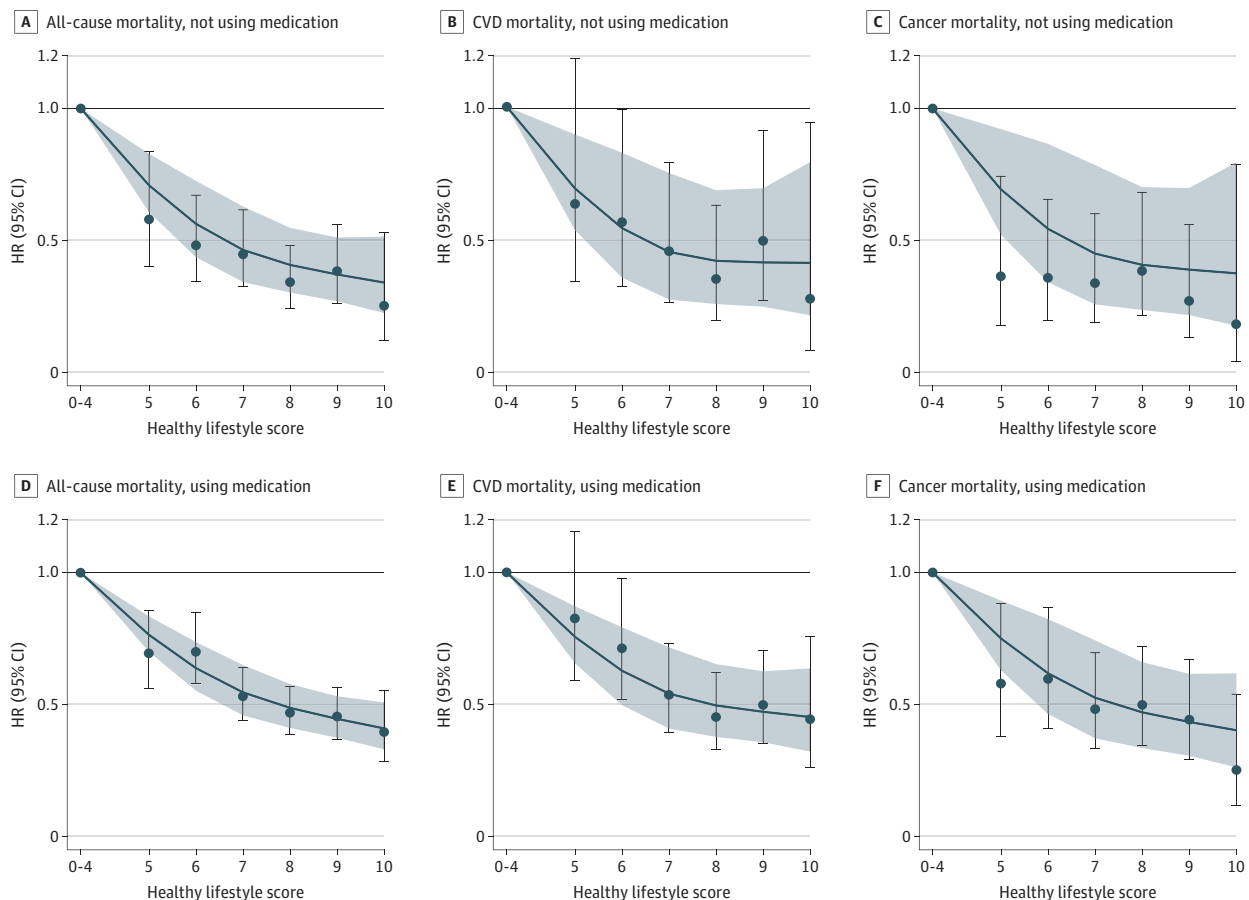
Lines indicate hazard ratios (HRs) estimated by restricted cubic spline model, considering reference as the mean lifestyle score among participants with 0-4 points; and shading, 95% CIs of estimated HRs.

Through linking to drug-dispensing records from community pharmacies and hospital discharge records, a study in the Netherlands identified 2325 participants aged 40 to 59 years who initiated antihypertensive medication. They found that 22% of participants temporarily stopped and restarted using medication and only 39% of participants used the medication continuously during 10 years of follow-up.[27] According to a systematic analysis of 968 419 adults from 90 countries, there were large global disparities in hypertension treatment and control.[28]

Adherence to antihypertensive medication is certainly an effective strategy to lower BP and prevent cardiovascular events.[29] The benefit would be greater along with lifestyle modification, which has been highlighted as the first-line treatment of hypertension in 2020 International Society of Hypertension Global Hypertension Practice Guidelines.[7] The UK Biobank study found that maintaining healthy lifestyle factors (BMI, diet, smoking, alcohol consumption, sodium excretion, and sedentary behavior) was associated with 3.5 mm Hg lower systolic BP and approximately 30% lower risk of CVD, regardless of genetic susceptibility to hypertension.[30] In addition, several randomized clinical trials among participants with nonoptimal BP or hypertension supported the beneficial effects of lifestyle modification on BP control and cardiovascular health. For example, in the PREMIER Clinical Trial of 810 participants with nonoptimal BP, lifestyle intervention through weight loss, sodium restriction, enhanced physical activity, limited alcohol intake, and improving dietary quality over 6 months significantly reduced systolic BP (by 4.3 mm Hg) and the risk of coronary heart disease (by 12%).[21,22] In the Chinese Hypertension Intervention Efficacy study, including 12 245 participants with hypertension, conducting a lifestyle intervention using health education over 3.5 years, found that participants with improvements in at least 2 lifestyle factors, including weight loss, increasing exercise, and healthy diet, had a 55% lower risk of cardiovascular events.[31]

Evidence regarding the joint association of antihypertensive medication and lifestyle with cardiovascular health is limited and somewhat mixed. A 2020 trial by Xiao et al[32] found that the combination of lifestyle and medication intervention led to better BP control than medication alone.

Table 3. All-Cause and Cause-Specific Mortality According to Changes in Lifestyle Score (2008-2013) Among Participants With Hypertension

Measure	Change in lifestyle score, HR (95% CI)			
	Consistently low	High to low	Low to high	Consistently high
Person-years, No.	2032	3236	3271	29 574
Participants, No.	308	607	595	5353
All-cause mortality				
Deaths, No.	65	100	49	409
Model 1[a]	1 [Reference]	0.92 (0.67-1.26)	0.51 (0.35-0.74)	0.47 (0.36-0.62)
Model 2[b]	1 [Reference]	0.95 (0.69-1.31)	0.53 (0.37-0.78)	0.52 (0.39-0.68)
Model 3[c]	1 [Reference]	0.94 (0.68-1.29)	0.52 (0.36-0.76)	0.51 (0.39-0.67)
CVD mortality				
Deaths, No.	29	49	21	170
Model 1[a]	1 [Reference]	1.03 (0.65-1.65)	0.50 (0.28-0.88)	0.46 (0.31-0.69)
Model 2[b]	1 [Reference]	1.08 (0.68-1.73)	0.54 (0.31-0.96)	0.53 (0.35-0.79)
Model 3[c]	1 [Reference]	1.06 (0.66-1.70)	0.53 (0.30-0.94)	0.51 (0.34-0.77)
Cancer mortality				
Deaths, No.	16	24	18	107
Model 1[a]	1 [Reference]	0.88 (0.47-1.67)	0.71 (0.36-1.39)	0.48 (0.28-0.82)
Model 2[b]	1 [Reference]	0.93 (0.49-1.75)	0.73 (0.37-1.44)	0.51 (0.30-0.86)
Model 3[c]	1 [Reference]	0.94 (0.50-1.79)	0.73 (0.37-1.44)	0.52 (0.30-0.89)

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.

[a] Adjusted for age (continuous), and sex (male vs female).

[b] Further adjusted for education attainment (<high school, high school or equivalent, ≥college), drinking status (never drinker, former drinker, or current drinker), hypertension duration (≤5, >5 to 10, or >10 years), self-reported physician-diagnosed CVD (yes or no) and diabetes (yes or no), and uses of hypoglycemic (yes or no) or lipid-lowering (yes or no) medication.

[c] Further adjusted for systolic blood pressure (continuous), diastolic blood pressure (continuous), fasting glucose (continuous), HDL cholesterol (continuous), and eGFR (continuous).

However, 2 cross-sectional studies reported no significant association between lifestyle and BP control for participants who were using antihypertensive medication.[33,34] In addition, 2 observational studies in Finland reported that participants with hypertension who were not using antihypertensive medication but adopted at least 3 healthy behaviors (never smoking, weight within reference range, moderate or vigorous exercise, vegetable consumption ≥3 times/week, and limited alcohol intake) had significantly lower risk of stroke or heart failure compared with those using antihypertensive medication but following fewer than 3 healthy behaviors.[14,15] Notably, these studies were mostly performed among Western populations, and some studies were limited by small sample size, cross-sectional study design, simple and noncomprehensive assessment on overall lifestyle, no information on changes in lifestyle, and insufficient adjustment for several important covariates, such as duration of hypertension and comorbidity.

Additionally, to our knowledge, no study has examined the combined association of antihypertensive medication treatment and lifestyle with mortality risk among participants with hypertension. In this study, we found that individuals using antihypertensive medication and following a favorable lifestyle had the lowest risk of all-cause, CVD, and cancer mortality. There were inverse linear associations between lifestyle score and mortality, regardless of hypertensive medication use. Additionally, for participants with an unfavorable lifestyle, there was no significant reduction in mortality risk even if they were using antihypertensive medication. Furthermore, we found that improvement in lifestyle after hypertension diagnosis was associated with significantly lower risk of subsequent death. From a public health perspective, BP management and complication prevention have great health and socioeconomic benefits, considering that the annual cost of hypertension has reached tens of billions of dollars per country.[35] Adherence to an antihypertensive medication regimen is no doubt an efficient way to control BP; however, it is not advisable to only rely on medication and ignore the role of lifestyle for the prevention of poor prognosis. Our findings further support that the combination of antihypertensive medication treatment and adopting a healthier lifestyle (even for those with an unfavorable lifestyle at hypertension diagnosis but who improve it later) could maximize the health benefits.

To our knowledge, we are among the first to investigate the combinations of antihypertensive medication use and lifestyle, as well as changes in lifestyle, in association with risk of all-cause, CVD, and cancer mortality. The underlying mechanisms for the beneficial associations of these lifestyle behaviors may involve various pathways. Each behavior might have an impact on BP by modulating visceral fat accumulation, insulin resistance, rennin-angiotensin-aldosterone system, vascular endothelial function, oxidative stress, inflammation, and/or autonomic function.[12] A 10–mm Hg reduction in systolic BP or a 5–mm Hg reduction in diastolic BP was associated with 10% to 30% lower risk of major CVD events and 11% to 13% lower risk of all-cause mortality.[36,37] Besides the associations with BP, these lifestyle factors may have associations with CVD and deaths through a series of metabolic and molecular alterations manifested as inhibiting insulin resistance, inflammation, and oxidative stress and slowing the accumulation of cellular and organ damage.[38-42]

Limitations

This study has some limitations. First, we asked about hypertensive medication use within the last 2 weeks, which may not represent long-term medication adherence or whether the participants used the prescription on time. However, 74% of participants with hypertension had the same answer to antihypertensive medication use at baseline and first follow-up. In addition, there was no information on the number and dosage of antihypertensive medication; thus, we could not comprehensively evaluate the direct association of medication with blood pressure, which would require detailed investigation in future studies. Second, we believe our findings are generalizable to middle-aged and older Asian populations, but they would need to be replicated in other ethnicities and age groups. Third, the 5 factors included in the lifestyle score might not represent all aspects of lifestyle, although they were the major modifiable components and mainly reported in previous literatures. Additionally, we adjusted for comprehensive covariates, and the results remained consistent. Fourth,

diet was assessed using a simple food frequency questionnaire without information on portions size; hence, we were unable to assess total energy intake in the model. Nevertheless, the association of vegetable, fruit, and meat intake frequency with CVD risk was reported in another large prospective study of Chinese population.[43] Fifth, measurement errors were inevitable in self-reported assessments of lifestyle factors. However, owing to the prospective study design, the misclassifications would likely be nondifferential and tended to attenuate the observed association to null. Sixth, selection bias could be possible owing to the differences in baseline demographics, lifestyles, and comorbidities between participants included and excluded from this analysis. Seventh, owing to the observational study design, the residual confounding could not be completely ruled out.

Conclusions

This cohort study found that the combination of using antihypertensive medication and adhering to a favorable lifestyle was associated with significantly lower risk of all-cause, CVD, and cancer mortality. In addition, improvement in lifestyle after hypertension diagnosis was also associated with lower risk of mortality. Our findings highlight that, in addition to using antihypertensive medication, following a favorable lifestyle was associated with benefits in preventing or delaying premature death among individuals with hypertension. For the management of hypertension, advocating regular medication is important but not sufficient; long-term adherence to a favorable lifestyle may yield greater benefits.

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SUPPLEMENT.