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Blood Pressure and the Risk of Death From Non-cardiovascular Diseases: A Population-based Cohort Study of Korean Adults

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Objectives: The objective of this study was to assess the relationship between systolic and diastolic blood pressure (SBP, DBP) and the risk of death from specific causes other than cardiovascular diseases.

Methods: We calculated the risk of specific death by SBP and DBP categories for 506 508 health examinees in 2002-2003 using hazard ratios (HRs) and 95% confidence intervals (CIs) in a Cox proportional hazards model.

Results: Compared to normal levels (SBP <120 or DBP <90 mmHg), stage I systolic and diastolic hypertension (SBP 140-159, DBP 85-89 mmHg, respectively) were associated with an increased risk of death from diabetes mellitus, alcoholic liver disease, and renal failure (HR, 1.83; 95% CI, 1.51 to 2.22; HR, 1.24; 95% CI, 1.06 to 1.46; HR, 2.30; 95% CI, 1.64 to 3.21; HR, 1.67; 95% CI, 1.27 to 2.20; HR, 1.99; 95% CI, 1.41 to 2.81; HR, 1.31; 95% CI, 0.99 to 1.73, respectively), but a decreased risk of death from intestinal pneumonia (HR, 0.64; 95% CI, 0.42 to 0.98; HR, 0.59; 95% CI, 0.39 to 0.91). Only stage II systolic hypertension (SBP ≥160 mmHg) was associated with an increased risk of death from pneumonia, liver cirrhosis, and intestinal ischemia (HR, 1.54; 95% CI, 1.19 to 1.98; HR, 1.46; 95% CI, 1.00 to 2.15; HR, 3.77; 95% CI, 1.24 to 11.40, respectively), and stage I and II diastolic hypertension (SBP 140-159 and ≥160 mmHg) were associated with an increased risk of death from intestinal ischemia (HR, 3.07; 95% CI, 1.27 to 7.38; HR, 4.39; 95% CI, 1.62 to 11.88, respectively).

Conclusions: An increase in blood pressure levels may alter the risk of death from certain causes other than cardiovascular diseases, a well-known outcome of hypertension, although the mechanism of these associations is not well documented.

Key words: Hypertension, Cohort studies, Korean population, Blood pressure

INTRODUCTION

Hypertension is defined as a sustained elevation of systemic arterial blood pressure (BP). In last 16 years, the mean BP of the general Korean population has decreased, potentially leading to changes in health outcomes [1]. Hypertension is a well-verified risk factor of mortality from cardiovascular disease and heart failure [2,3]. In contrast, little has been reported about the relationship of hypertension with major causes of death other than cardiovascular and cerebrovascular mortality

in Korea or in other countries throughout the world.

Arterial hypertension is known to damage the vascular system, which extends to every organ and all tissues [4], meaning that some organs could share the same mechanism of damage as found in atherosclerosis. The heart, brain, eye, kidney, and arterial aneurysms are generally considered to be sensitive to damage from hypertension, and previous studies have examined the effects of arterial hypertension on these organs [5]. However, few studies have been conducted on other organs that may be affected by arterial hypertension, so the impact of arterial hypertension on other organs remains largely unclear.

The purpose of this study was to investigate the risk of death from specific causes other than well-known causes of death in subjects with hypertension compared to subjects with low BP using Korean large-scale health screening data.

METHODS

Data Collection and Study Population Selection

We used data from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS), a large-scale retrospective cohort (n=515 000) comprising a 10% random sample of all health examinees aged 40-70 years who participated in the National Health Insurance health screening program in 2002-2003 [6]. Information on systolic and diastolic BP (SBP and DBP), anthropometric indices (e.g., height, weight, and body mass index [BMI]), laboratory blood and urine test results, and self-reported questionnaire data were collected in the baseline year of 2002-2003, and the data were recollected biennially (annually for non-white collar workers). We excluded participants without information about their BP (n=336) and those who died within 2 years of cohort enrollment (n=4228). To account for the effects of BMI, a major confounder of the association between BP and death risk, we additionally excluded those who were extremely underweight (BMI < 15 kg/m^2), extremely obese (BMI > 50 kg/m^2), or did not have BMI information (n=637). Furthermore, participants with very high hemoglobin levels (>18.3 mg/dL) (n=310) were also excluded because the elevated risk of death due to high hemoglobin levels could be misinterpreted as a result of hypertension, since hemoglobin levels are positively correlated with BP and higher hemoglobin levels have shown an association with mortality [7,8].

Finally, a total of 506 508 subjects were included as the study population. Within this population, a total of 33 215 all-cause deaths occurred during up to 11 years of follow-up.

This study was reviewed and approved by the institutional review board (IRB) of Seoul National University Hospital (IRB no. 1806-149-953).

Outcome Variables

Information on death (date and cause of death) from Statistics Korea was individually linked using unique personal identification numbers [6]. The main outcomes for this study were all-cause death and specific death, except for (1) disease codes including well-known causes of death related to hypertension: cerebrovascular and cardiovascular diseases (I codes); (2) disease codes including causes of death that are less well-known to be associated with hypertension: neoplasms (all C and D codes), non-disease causes of death (S, T, V, Y codes), and causes of death related to pregnancy, the prenatal period, and congenital abnormalities (O, P, R codes); and (3) cases affected by the masking policy of the NHIS-HEALS public open data: mental, behavioral and neurodevelopmental disorders (F codes), as defined by the International Classification of Diseases, 10th Revision (ICD-10). We included individual causes of death for which at least 40 deaths were observed for a single ICD-10 disease code in the study population: (1) tuberculosis (A15-A19; n=261), hepatitis (B15-B19; n=148); (2) diabetes mellitus (DM; E11-E14; n=1203), including non-insulin-dependent DM (E11; n=793); (3) Parkinson disease (G20; n=287), Alzheimer disease (G30; n=195); (4) pneumonia (J12-J19; n=783), interstitial pneumonia (J84; n=187), chronic obstructive pulmonary disease (J43-J44; n=130), aspiration pneumonia (J69; n=857); (5) alcoholic liver disease (ALD; K70; n=388), liver cirrhosis (LC; K74; n=357), intestinal ischemia (vascular disorders of intestine; K55; n=40), paralytic ileus except hernia (K56; n=41), pancreatitis (K85-86; n=49), including acute pancreatitis (K85; n=40); (6) renal failure (RF; N17-N19; n=378), including chronic renal failure (CRF; N18; n=294), and acute renal failure (ARF; N17; n=48) (Table S1). The follow-up period of each individual was defined as from the day of study enrollment to the date of death (if applicable) or December 31, 2013.

Exposure Variables

All participants underwent medical examinations at local hospitals. A standard sphygmomanometer was used to measure BP in a seated position, and the SBP and DBP were measured as the first and last Korotkoff sounds, respectively [6]. We used SBP and DBP data measured on the day of study en-

Table 1. Selected characteristics by systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a retrospective cohort of participants enrolled in the Korea National Health Insurance-Health Screening in 2002-2003, followed through 2013

Characteristics	Cohort (n=506 508)	SBP (mmHg)				DBP (mmHg)			
		<120 (n=146 340)	120-139 (n=224 798)	140-159 (n=103 816)	≥160 (n=31 544)	<80 (n=198 162)	80-89 (n=175 483)	90-99 (n=95 975)	≥100 (n=36 888)
Age (y)	51 (45-60)	48 (44-56)	50 (44-60)	55 (48-64)	59 (50-66)	50 (44-58)	51 (45-60)	53 (46-62)	54 (47-62)
BMI (kg/m²)	23.9 (22.0-25.9)	23.1 (21.3-24.9)	24.0 (22.2-25.9)	24.6 (22.7-26.6)	24.8 (22.9-26.9)	23.3 (21.5-25.2)	24.0 (22.1-25.9)	24.5 (22.7-26.5)	25.0 (23.1-27.0)
Male	274 077 (54.1)	65 533 (44.8)	129 611 (57.7)	61 134 (58.9)	17 799 (56.4)	89 282 (45.1)	101 398 (57.8)	59 903 (62.4)	23 494 (63.7)
Diabetes mellitus[1]	39 766 (7.9)	6753 (4.6)	16 961 (7.5)	11 550 (11.1)	4502 (14.3)	11 585 (5.9)	14 151 (8.1)	9766 (10.2)	4264 (11.6)
Current anemia[2]	47 779 (9.4)	18 151 (12.4)	19 035 (8.5)	8059 (7.8)	2534 (8.0)	24 402 (12.3)	14 447 (8.2)	6666 (7.0)	2264 (6.1)
Personal history									
Hypertension	42 298 (8.4)	3233 (2.2)	14 758 (6.6)	16 236 (15.6)	8071 (25.6)	7905 (4.0)	13 909 (7.9)	12 821 (13.4)	7663 (20.8)
Heart disease	7197 (1.4)	1666 (1.1)	2724 (1.2)	1774 (1.7)	1033 (3.3)	2718 (1.4)	2449 (1.4)	1474 (1.5)	556 (1.5)
Stroke	2316 (0.5)	367 (0.3)	874 (0.4)	731 (0.7)	344 (1.1)	639 (0.3)	874 (0.5)	570 (0.6)	233 (0.6)
Diabetes mellitus	21 241 (4.2)	4228 (2.9)	9271 (4.1)	5797 (5.6)	1945 (6.2)	7345 (3.7)	7651 (4.4)	4551 (4.7)	1694 (4.6)
Family history									
Cancer	60 888 (12.0)	20 728 (14.2)	27 224 (12.1)	10 378 (10.0)	2558 (8.1)	26 454 (13.3)	20 519 (11.7)	10 433 (10.9)	3482 (9.4)
Hypertension	41 152 (8.1)	9729 (6.7)	17 813 (8.0)	10 196 (9.8)	3414 (10.8)	13 387 (6.8)	14 202 (8.1)	9253 (9.6)	4310 (11.7)
Heart disease	13 979 (2.8)	4366 (3.0)	6304 (2.8)	2681 (2.6)	628 (2.0)	5524 (2.8)	4898 (2.8)	2603 (2.7)	954 (2.6)
Stroke	27 109 (5.4)	7652 (5.2)	12 279 (5.5)	5686 (5.5)	1492 (4.7)	10 080 (5.1)	9496 (5.4)	5432 (5.7)	2101 (5.7)
Diabetes mellitus	31 133 (6.2)	10 107 (7.0)	14 110 (6.3)	5517 (5.3)	1399 (4.4)	13 002 (6.6)	10 896 (6.2)	5322 (5.6)	1913 (5.2)
Ever smoker[3]	159 529 (31.5)	41 072 (28.1)	75 127 (33.4)	33 715 (32.5)	9615 (30.5)	54 976 (27.7)	58 173 (33.2)	33 504 (34.9)	12 876 (34.9)
Alcohol drinking[4]	57 016 (11.3)	11 238 (7.7)	25 832 (11.5)	14 753 (14.2)	5193 (16.5)	16 326 (8.2)	20 590 (11.7)	13 797 (14.4)	6303 (17.1)
Low physical activity[5]	282 688 (55.8)	83 219 (56.9)	122 933 (54.7)	57 785 (55.7)	18 751 (59.4)	113 454 (57.3)	97 242 (55.4)	51 831 (54.0)	20 161 (54.7)

Values are presented as median (interquartile range) or number (%).
The differences in the distribution of specific variables by SBP and DBP categories were tested with the chi-square test for categorical variables and analysis of variance for continuous variables; The results of the distribution difference test were all significant, regardless of SBP or DBP (all p-values<0.01).
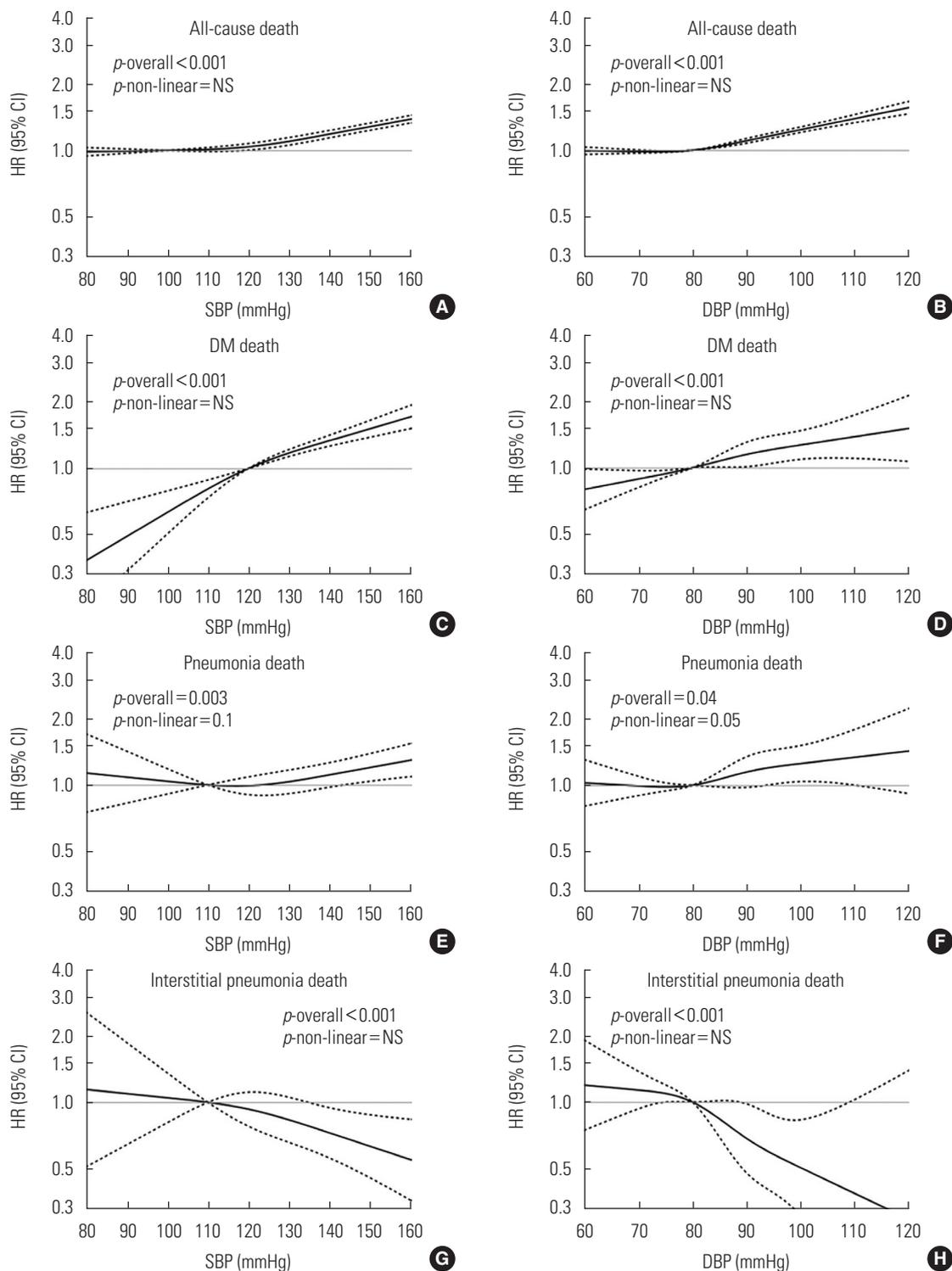[1] Fasting blood sugar levels >125 mg/dL.
[2] Hemoglobin of <13 mg/dL in men and hemoglobin of <12 mg/dL in women.
[3] Current and past cigarette smoker.
[4] Alcohol drinking >2 times/wk.
[5] Low physical activity ≤2 times/wk.

Figure 1. Restricted cubic spline graphs for the risk of all-cause and specific death by SBP (A: all-cause, C: DM, E: pneumonia, G: interstitial pneumonia, I: alcoholic liver disease, K: liver cirrhosis, M: intestinal ischemia, and O: chronic renal failure; 3 knots at 100, 120, and 140 mmHg; 120 mmHg as a reference) and DBP (B: all-cause, D: DM, F: pneumonia, H: interstitial pneumonia, J: alcoholic liver disease, L: liver cirrhosis, N: intestinal ischemia, and P: chronic renal failure; 4 knots at 70, 80, 90, 100 mmHg; 80 mmHg as a reference). Hazard ratios (HRs) and 95% Confidence intervals (Cis) were estimated in Cox proportional hazard models adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, physical activity, current anemia, chronic disease score in the participant's medical history, and chronic disease score in the family history. SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, non-specific; DM, diabetes mellitus.
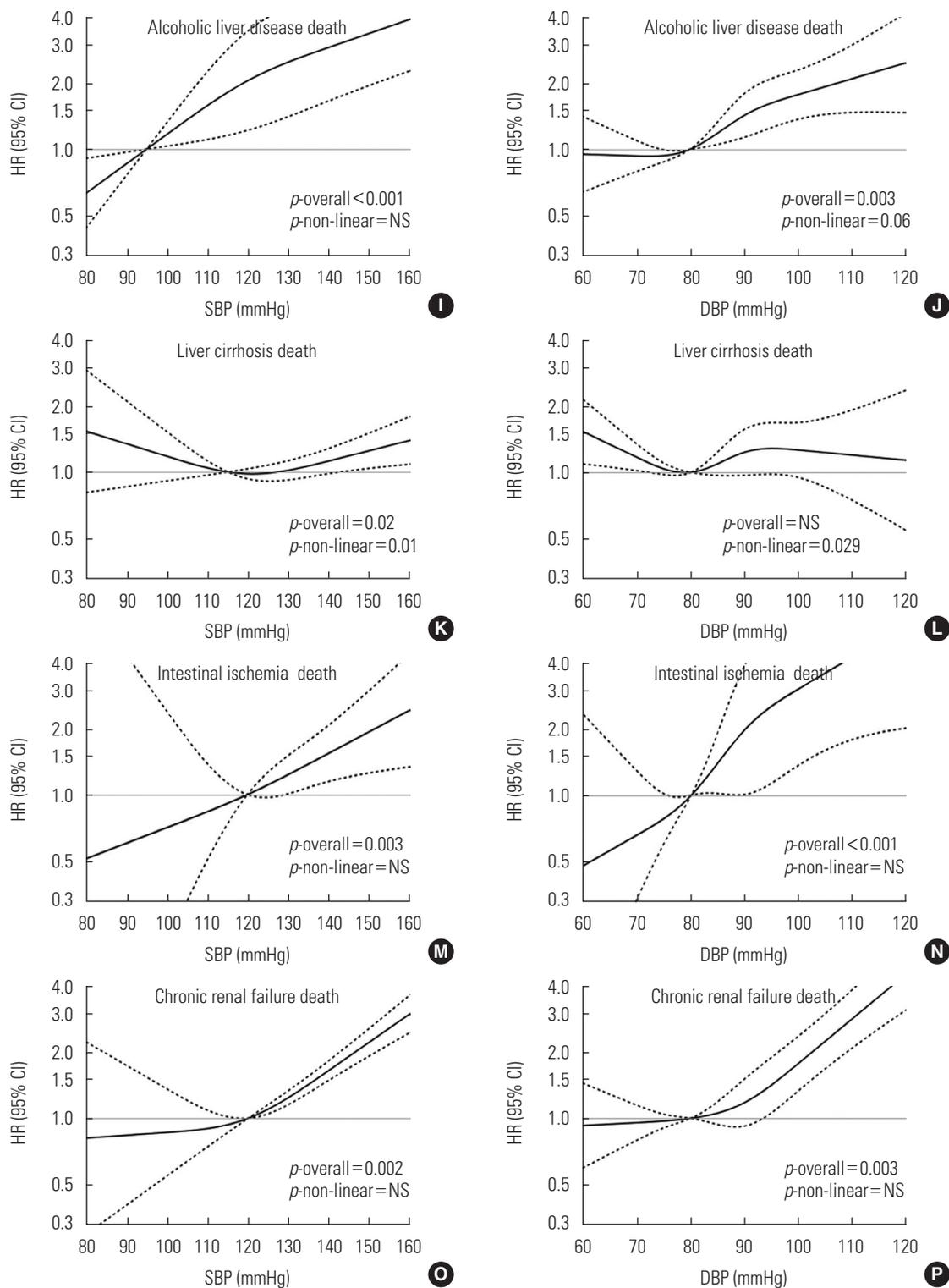
Figure 1. Continued from the previous page.

rollment as the main explanatory variable.

The SBP and DBP levels were classified into 4 groups, as follows: stage II hypertension (SBP ≥160 or DBP ≥100 mmHg), stage I hypertension (SBP 140-159 or DBP 90-99 mmHg), BP elevation (SBP 120-139 or DBP 80-89 mmHg), and normal BP as a reference category (SBP <120 and DBP <80 mmHg), following the guidelines of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and

Treatment of High Blood Pressure [9]. To observe the association of the combined effect of SBP and DBP on the risk of death, we classified each BP variable into a binary variable of hypertension and non-hypertension, and combined them into the following 4 categories: SBP ≥140 and DBP ≥90, SBP ≥140 and DBP <90, SBP <140 and DBP ≥90, and SBP <140 and DBP <90 mmHg.

Statistical Analysis

Differences in characteristics among different BP groups were evaluated using the chi-square test for categorical variables and 1-way analysis of variance for continuous variables. The associations between BP levels and the risk of death from each cause were assessed in Cox proportional hazards models adjusted for all significant confounders, as shown in Table 1. The confounders adjusted in the Cox proportional hazards models were as follows: age at entry (continuous), sex, smoking status (never vs. ever), alcohol intake (0-1, 2-4, ≥5 times/wk),

physical activity (no, rarely, yes), BMI (<18.0, 18.0-22.9, 23.0-29.9, ≥30.0 kg/m²), chronic disease score in the family history, and chronic disease score in the participant's individual medical history. The chronic disease score in the family history was calculated as the sum of binary scores for a family history of 5 major chronic diseases (hypertension, heart disease, stroke, DM, and cancer) (no=0, yes=1), and the chronic disease score for each individual participant was calculated as the sum of binary scores for a prior history of 4 major chronic diseases (hypertension, heart disease, stroke, and DM) (no=0, yes=1). Cubic spline figures for the associations between SBP or DBP levels (continuous scales) and the risk of each cause of death were used to examine non-linear effects in each association. When there was a suspicious threshold on the spline graph, we used piecewise linear models to fit non-linearity across all possible thresholds. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 2. Associations between the categories of SBP and all-cause and specific death in a retrospective cohort enrolled in the Korea National Health Insurance-Health Screening in 2002-2003, followed through 2013

	Total death (n)	SBP (mmHg)							*p* for trend
		<120	120-139		140-159		≥160		
		Death (n)	Death (n)	HR (95% CI)[1]	Death (n)	HR (95% CI)[1]	Death (n)	HR (95% CI)[1]	
All-cause	33 215	6187	13 256	1.09 (1.06, 1.12)	9527	1.22 (1.18, 1.26)	4245	1.46 (1.41, 1.52)	<0.01
Tuberculosis	261	57	104	0.95 (0.69, 1.31)	66	0.91 (0.64, 1.31)	34	1.24 (0.80, 1.92)	0.58
Hepatitis	148	29	68	1.38 (0.89, 2.15)	37	1.39 (0.84, 2.31)	14	1.56 (0.80, 3.03)	0.17
DM, total	1203	146	478	1.63 (1.35, 1.96)	382	1.83 (1.51, 2.22)	197	2.38 (1.91, 2.96)	<0.01
NIDDM	793	102	309	1.52 (1.21, 1.91)	256	1.77 (1.40, 2.24)	126	2.21 (1.69, 2.89)	<0.01
Parkinson disease	287	46	134	1.36 (0.97, 1.91)	75	1.06 (0.73, 1.54)	32	1.16 (0.73, 1.84)	0.93
Alzheimer disease	195	37	84	1.08 (0.73, 1.60)	44	0.76 (0.48, 1.18)	30	1.24 (0.76, 2.03)	0.9
Pneumonia	783	132	310	1.12 (0.91, 1.37)	222	1.11 (0.89, 1.39)	119	1.54 (1.19, 1.98)	<0.01
Interstitial pneumonia	187	45	84	0.82 (0.57, 1.18)	47	0.64 (0.42, 0.98)	11	0.38 (0.20, 0.75)	<0.01
Aspiration pneumonia	130	24	52	1.04 (0.64, 1.70)	32	0.90 (0.52, 1.54)	22	1.58 (0.87, 2.85)	0.33
COPD	857	192	341	0.91 (0.76, 1.08)	231	0.89 (0.73, 1.08)	93	0.94 (0.73, 1.21)	0.45
Alcoholic liver disease	388	54	181	1.88 (1.39, 2.56)	107	2.30 (1.64, 3.21)	46	3.14 (2.09, 4.72)	<0.01
Liver cirrhosis	357	74	136	0.98 (0.74, 1.31)	102	1.23 (0.90, 1.67)	45	1.46 (1.00, 2.15)	0.02
Intestinal ischemia	39	5	18	1.81 (0.67, 4.92)	6	0.88 (0.26, 2.95)	10	3.77 (1.24, 11.40)	0.10
Paralytic ileus except hernia	41	7	18	1.14 (0.47, 2.75)	6	0.49 (0.16, 1.47)	10	1.91 (0.71, 5.17)	0.61
Pancreatitis	49	10	22	1.13 (0.53, 2.40)	14	1.15 (0.50, 2.66)	3	0.68 (0.18, 2.53)	0.79
Acute pancreatitis	40	7	18	1.29 (0.54, 3.12)	12	1.38 (0.53, 3.60)	3	0.95 (0.24, 3.78)	0.85
Renal failure	378	46	116	1.26 (0.89, 1.77)	127	1.99 (1.41, 2.81)	89	3.60 (2.49, 5.20)	<0.01
Chronic renal failure	294	33	90	1.36 (0.91, 2.03)	95	2.07 (1.38, 3.10)	76	4.27 (2.80, 6.51)	<0.01
Acute renal failure	48	9	14	0.75 (0.32, 1.74)	16	1.23 (0.53, 2.84)	9	1.80 (0.69, 4.66)	0.11

SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus; COPD, chronic obstructive pulmonary disease.

[1]Adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, and physical activity, current anemia, chronic disease score in the participant's medical history, and chronic disease score in the family history.

RESULTS

Of the total subjects, 26.7% (n = 135 360) had systolic hypertension (SBP ≥ 140 mmHg) and 31.3% (n = 158 579) had diastolic hypertension (DBP ≥ 90 mmHg). Participants in the higher BP groups were older ($p<0.01$) and had higher serum cholesterol levels than those in the lower BP groups ($p<0.01$). Both the higher SBP and DBP groups had more subjects with a history of diabetes, heart disease, and stroke (all $p<0.01$). However, anemia was more prevalent in the lower SBP and DBP groups (all $p<0.01$). Figure 1 shows the estimated risk for each cause of death in relation to SBP or DBP levels. When adjusted for all potential confounders, the associations of each specific death risk with both SBP and DBP levels were linear, except for LC. Pneumonia had an overall linear effect but a mild non-linear effect (p-non-linearity = 0.03 for SBP; 0.049 for DBP), and LC had a non-linear effect in the association with SBP and DBP (p-non-linearity = 0.01 and 0.029, respectively).

As both SBP and DBP levels increased, the risk of death from DM, pneumonia, ALD, and RF increased steadily (p for trend < 0.05 for all), while the risk of death from interstitial pneumonia decreased ($p<0.01$). The risk of LC death was associated with only increasing SBP ($p=0.02$), and the risk of death from intestinal ischemia was only associated with increasing DBP ($p<0.01$) (Tables 2 and 3).

Compared to people with normal SBP, those with stage I systolic hypertension had higher risks for death from DM, ALD, and RF (hazard ratio [HR], 1.83; 95% CI, 1.51 to 2.22; HR, 2.30; 95% CI, 1.64 to 3.21; HR, 1.99; 95% CI, 1.41 to 2.81, respectively) and those with stage II systolic hypertension had much higher risks for death from these causes (HR, 2.38 for DM; HR, 3.14 for ALD, and HR, 3.60 for RF, respectively). Of particular note, the risk of death from DM and ALD increased even with SBP elevation (SBP 120-139 mmHg). The risk of death from pneumonia, LC, and intestinal ischemia was significantly higher in only the stage II systolic hypertension group (HR, 1.54;

Table 3. Associations between the categories of DBP and all-cause and specific death in a retrospective cohort enrolled in the Korea National Health Insurance-Health Screening in 2002-2003, followed through 2013

	Total death (n)	DBP (mmHg)							*p* for trend
		<80	80-89		90-99		≥100		
		Death (n)	Death (n)	HR (95% CI)[1]	Death (n)	HR (95% CI)[1]	Death (n)	HR (95% CI)[1]	
All-cause	33 215	10 953	11 291	1.05 (1.02, 1.08)	7506	1.15 (1.11, 1.18)	3465	1.31 (1.26, 1.36)	<0.01
Tuberculosis	261	101	73	0.78 (0.58, 1.06)	59	1.07 (0.77, 1.48)	28	1.29 (0.84, 1.97)	0.26
Hepatitis	148	52	46	0.94 (0.63, 1.40)	34	1.20 (0.77, 1.87)	16	1.04 (0.79, 2.49)	0.13
DM, total	1203	372	411	1.13 (0.98, 1.30)	284	1.24 (1.06, 1.46)	136	1.42 (1.16, 1.73)	<0.01
NIDDM	793	246	272	1.14 (0.96, 1.36)	181	1.21 (1.00, 1.48)	94	1.50 (1.18, 1.91)	<0.01
Parkinson disease	287	111	94	0.87 (0.66, 1.15)	68	1.02 (0.75, 1.39)	14	0.52 (0.30, 0.91)	0.17
Alzheimer disease	195	64	75	1.30 (0.93, 1.81)	45	1.29 (0.88, 1.90)	11	0.82 (0.43, 1.56)	0.77
Pneumonia	783	258	272	1.12 (0.94, 1.33)	184	1.24 (1.03, 1.50)	69	1.18 (0.90, 1.55)	0.03
Interstitial pneumonia	187	75	72	0.91 (0.66, 1.26)	30	0.59 (0.39, 0.91)	10	0.48 (0.25, 0.93)	<0.01
Aspiration pneumonia	130	41	44	1.16 (0.76, 1.78)	31	1.35 (0.84, 2.17)	14	1.56 (0.85, 2.89)	0.11
COPD	857	316	286	1.00 (0.85, 1.17)	185	1.09 (0.91, 1.31)	70	1.06 (0.82, 1.38)	0.25
Alcoholic liver disease	388	106	122	1.11 (0.86, 1.44)	107	1.67 (1.27, 2.20)	53	2.07 (1.48, 2.90)	<0.01
Liver cirrhosis	357	127	121	0.96 (0.74, 1.23)	74	0.96 (0.71, 1.28)	35	1.07 (0.73, 1.57)	0.84
Intestinal ischemia	39	8	9	1.20 (0.46, 3.11)	14	3.07 (1.27, 7.38)	8	4.39 (1.62, 11.88)	<0.01
Paralytic ileus except hernia	41	14	14	0.99 (0.47, 2.09)	6	0.66 (0.25, 1.74)	7	1.86 (0.74, 4.67)	0.46
Pancreatitis	49	18	20	1.10 (0.58, 2.09)	7	0.63 (0.26, 1.52)	4	0.87 (0.29, 2.60)	0.44
Acute pancreatitis	40	14	18	1.25 (0.62, 2.52)	4	0.45 (0.15, 1.38)	4	1.08 (0.35, 3.34)	0.52
Renal failure	378	115	115	1.03 (0.80, 1.34)	90	1.31 (0.99, 1.73)	58	2.04 (1.48, 2.81)	<0.01
Chronic renal failure	294	91	84	0.95 (0.71, 1.28)	73	1.33 (0.97, 1.81)	46	2.01 (1.40, 2.88)	<0.01
Acute renal failure	48	15	18	1.21 (0.61, 2.42)	7	0.77 (0.31, 1.90)	8	2.16 (0.90, 5.17)	0.34

DBP, diastolic blood pressure; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus; COPD, chronic obstructive pulmonary disease.
[1]Adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, and physical activity, current anemia, chronic disease score in the participant's medical history, and chronic disease score in the family history.

95% CI, 1.19 to 1.98; HR, 1.46; 95% CI, 1.00 to 2.15; HR, 3.77; 95% CI, 1.24 to 11.40). People with stage I systolic hypertension were at a reduced risk for death from interstitial pneumonia (HR, 0.64; 95% CI, 0.42 to 0.98), and those with stage II systolic hypertension were at a much lower risk (HR, 0.38; 95% CI, 0.20 to 0.75) (Table 2).

Compared to people with normal DBP, those with stage I diastolic hypertension had an increased risk for death from DM, ALD, RF, and intestinal ischemia (HR, 1.24; 95% CI, 1.06 to 1.46; HR, 1.67; 95% CI, 1.27 to 2.20; HR, 1.31; 95% CI, 0.99 to 1.73; HR, 3.07; 95% CI, 1.27 to 7.38, respectively). Stage II diastolic hypertension was associated with a much higher risk of death from DM, ALD, RF, and intestinal ischemia (HR, 1.42, 2.07, 2.04, 4.39; respectively). The risk of pneumonia death was increased in individuals with stage I diastolic hypertension, but not those with stage II diastolic hypertension. Stage I and II diastolic hypertension were associated with a decreased risk for death from interstitial pneumonia (HR, 0.59; 95% CI, 0.39 to 0.91; HR, 0.48; 95% CI, 0.25 to 0.93) (Table 3).

Compared to the reference group (SBP <140 and DBP <90 mmHg), the presence of only diastolic hypertension increased the risk of death from ALD and intestinal ischemia (HR, 1.46; 95% CI, 1.03 to 2.07; HR, 3.61; 95% CI, 1.42 to 9.20, respectively). Compared to the reference group, the presence of only systolic hypertension increased the risk of death from DM and RF (HR, 1.39; 95% CI, 1.19 to 1.63; HR, 2.09; 95% CI, 1.59 to 2.76, respectively) compared to both normal SBP and DBP levels, but the risk of death from both diseases was not further increased by the presence of both systolic and diastolic hypertension (HR, 1.39 and 2.17, respectively). Deaths from 2 types of pneumonia (pneumonia and interstitial pneumonia) showed associations with only the presence of both types of hypertension (HR, 1.19; 95% CI, 1.00 to 1.41; HR, 0.51; 95% CI, 0.34 to 0.77, respectively). For the risk of death from LC, the presence of only systolic hypertension without diastolic hypertension was associated with a decreased risk (HR, 0.56; 95% CI, 0.32 to 0.99), but the other categories were not associated with the risk of death from LC (Table 4).

Table 4. The combined effect of SBP and DBP on all-cause and specific death in a retrospective cohort enrolled in the Korea National Health Insurance-Health Screening in 2002-2003, followed by 2013

	SBP <140, DBP <90	SBP <140, DBP ≥90	SBP ≥140, DBP <90	SBP ≥140, DBP ≥90	*p*-value
All-cause	1.00 (reference)	1.05 (1.00, 1.10)	1.16 (1.12, 1.20)	1.25 (1.21, 1.28)	<0.01
Tuberculosis	1.00 (reference)	1.07 (0.63, 1.82)	0.75 (0.50, 1.13)	1.23 (0.92, 1.64)	0.40
Hepatitis	1.00 (reference)	1.60 (0.92, 2.79)	1.16 (0.67, 2.01)	1.24 (0.82, 1.86)	0.28
DM, total	1.00 (reference)	1.06 (0.82, 1.38)	1.39 (1.19, 1.63)	1.39 (1.21, 1.59)	<0.01
NIDDM	1.00 (reference)	1.08 (0.78, 1.49)	1.42 (1.17, 1.73)	1.39 (1.18, 1.65)	<0.01
Parkinson diseases	1.00 (reference)	0.91 (0.54, 1.55)	0.81 (0.57, 1.15)	0.90 (0.67, 1.20)	0.31
Alzheimer disease	1.00 (reference)	1.31 (0.72, 2.38)	0.82 (0.55, 1.24)	0.90 (0.63, 1.29)	0.42
Pneumonia	1.00 (reference)	1.20 (0.88, 1.63)	1.12 (0.91, 1.36)	1.19 (1.00, 1.41)	0.05
Interstitial pneumonia	1.00 (reference)	0.82 (0.44, 1.53)	0.88 (0.58, 1.33)	0.51 (0.34, 0.77)	<0.01
Aspiration pneumonia	1.00 (reference)	1.10 (0.50, 2.40)	0.77 (0.44, 1.33)	1.26 (0.84, 1.89)	0.47
COPD	1.00 (reference)	1.01 (0.74, 1.37)	0.84 (0.68, 1.03)	1.05 (0.89, 1.24)	0.98
Alcoholic liver disease	1.00 (reference)	1.46 (1.03, 2.07)	1.19 (0.81, 1.74)	1.83 (1.45, 2.31)	<0.01
Liver cirrhosis	1.00 (reference)	0.56 (0.32, 0.99)	1.28 (0.94, 1.76)	1.22 (0.95, 1.57)	0.07
Intestinal ischemia	1.00 (reference)	3.61 (1.42, 9.20)	-	2.15 (1.07, 4.33)	0.14
Paralytic ileus except hernia	1.00 (reference)	0.89 (0.21, 3.78)	0.64 (0.24, 1.70)	0.92 (0.44, 1.92)	0.66
Pancreatitis	1.00 (reference)	0.88 (0.27, 2.91)	1.45 (0.67, 3.12)	0.67 (0.30, 1.49)	0.57
Acute pancreatitis	1.00 (reference)	0.35 (0.05, 2.58)	1.54 (0.67, 3.52)	0.70 (0.30, 1.65)	0.68
Renal failure	1.00 (reference)	1.06 (0.63, 1.79)	2.09 (1.59, 2.76)	2.06 (1.62, 2.62)	<0.01
Chronic renal failure	1.00 (reference)	1.14 (0.64, 2.02)	2.15 (1.57, 2.94)	2.17 (1.65, 2.85)	<0.01
Acute renal failure	1.00 (reference)	0.44 (0.06, 3.30)	1.83 (0.87, 3.83)	1.44 (0.73, 2.85)	0.17

Values are presented as hazard ratio (95% confidence interval).
Hazard ratios were adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, physical activity, current anemia, chronic disease score in the participant's medical history, and chronic disease score in the family history.
SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus; COPD, chronic obstructive pulmonary disease.

DISCUSSION

In our study, as BP levels increased, the risk of death from DM, pneumonia, ALD, intestinal ischemia, and RF increased linearly, while the risk of death from interstitial pneumonia decreased linearly. The risk of LC death showed a non-linear association with BP levels. Stage I systolic or diastolic hypertension was associated with an increased risk of death from DM, ALD, and RF, relative to the corresponding normal BP levels, but was associated with a decreased risk of death from interstitial pneumonia. Stage II systolic and diastolic hypertension were associated with a much higher risk of death from DM, ALD, and RF. The risk of death from pneumonia and LC was only elevated in participants with stage II systolic hypertension. Death from intestinal ischemia was associated with stage II systolic hypertension and stage I and II diastolic hypertension. In the assessment of the combined risk of SBP and DBP for death, the risk of death from DM and RF increased with systolic hypertension alone, but the risk of death from ALD and intestinal ischemia was increased only by diastolic hypertension. The risk of death from pneumonia and interstitial pneumonia showed an association with the comorbidity of both systolic and diastolic hypertension.

Hypertension and DM are known to involve the same vascular complications and target organs [10,11]. Insulin resistance is the key feature of the pathogenesis of DM, and is also known to be associated with hypertension by several mechanisms that are closely related to vascular wall activity [12]. Compared with the general population, individuals with hypertension are more likely to have DM, and those with DM are also more likely to have hypertension [10,11]. In Korea, only 25.9% of patients with hypertension have diabetes, but 50% of patients with diabetes have hypertension [13,14]. In the latter group, diabetes may have been diagnosed earlier than hypertension, and diabetes may be recognized as the primary cause of death in the death certificate data. Therefore, we further analyzed our data to eliminate this possibility after excluding subjects with a past history of DM. In the results of the restricted analysis, which only included subjects with no past history of DM, individuals with systolic or diastolic hypertension had a higher risk of diabetes death than their counterparts with normal BP (Table S2).

Long-term persistence of hypertension leads to renal damage, resulting in chronic renal disease [15]. Secondary hypertension may also occur as a sequela of chronic renal disease,

even if hypertension does not occur first [15]. The increased risk of RF in hypertension patients is biologically plausible.

It is known that malignant systemic hypertension can aggravate underlying chronic kidney disease (CKD) rapidly. Uncontrolled high BP can cause damage to arteries around the kidney, which leads to decreased blood flow to kidney tissue [15,16]. However, controversy has long existed regarding whether mild-to-moderate elevation in systemic BP often triggers CKD [17]. Recent studies have showed that high-risk genes, such as *APOL1* in the African-American population, are associated with both focal segmental glomerulosclerosis and secondary hypertension [18,19]. Further studies of genetic markers are required to reveal the underlying mechanism.

In our study, an increased risk of death from ALD was prominently found in individuals with high DBP, with a dose-dependent trend. In Korea, hypertension is known to be related to alcohol consumption patterns [20], which can affect heart and cardiac end-diastolic pressure. Patients with alcoholic fatty liver often present with increased BP [21]. We suggest that ALD and hypertension share the common risk factor of alcohol, which may increase the risk of ALD mortality in hypertension patients, in particular those with diastolic hypertension, compared to people with low BP levels. Contrarily, the hemodynamic characteristics of LC involve vasodilation, which leads to low arterial BP [21]. It can be expected that low BP levels result from the hemodynamics of LC. If blood vessels function properly, arterial hypertension may occur in patients with early LC according to the natural history of LC, but BP falls to normal levels as LC progresses [22]. However, about 15% of LC patients are reported to have hypertension due to alteration of vasodilatation and vasoconstriction through dysfunctions in the circulatory system [21]. Patients with bleeding tendency due to end-stage LC are at a higher risk of fatal bleeding. It is possible that, in our study, high baseline SBP increased the future risk of vascular rupture. The decreased risk in the high DBP-only group could also be explained in terms of fatal bleeding. The lowest risk of death from LC was found in individuals with high DBP and normal SBP, which corresponds to a considerably low pulse pressure, a good predictor for stroke and other vascular accidents [23]. The spline graph between LC mortality and BP showed a non-linear association, suggesting that complex hemodynamic characteristics affect the relationship between LC and hypertension. In this study, we did not observe a relationship between BP levels in LC patients and mortality risk after LC diagnosis, it is necessary to further

examine the relationship between BP levels after LC diagnosis and the risk of death.

Although a direct relationship between pneumonia and essential hypertension has not been well established [24], there might be an indirect relationship. The incidence of pneumonia in the acute stage after stroke diagnosis is common as an acute complication of stroke and silent infarction, leading to sudden death [25-27]. Unlike pneumonia, no report indicating that high BP increased the risk of mortality from interstitial pneumonia was found in the literature. The lower risk of death from interstitial pneumonia observed in our cohort in individuals with hypertension may have been a coincidence, and this possibility should be investigated in larger cohort studies.

Intestinal ischemia is associated with acute or chronic low blood flow to the gut due to atherosclerosis, cardiac arrhythmias and other reasons. Although arterial hypertension is not a direct risk factor for intestinal ischemia in terms of gastrointestinal vascular pathology, several experimental results have shown that blood vessels in hypertensive animals are more sensitive to vasoconstrictors [28]. These results suggest that hypertension may induce intestinal ischemia and increase the risk of death in the presence of any stress conditions, although it is not a common mechanism of intestinal ischemia. In this study, this risk was more closely related to DBP than SBP. Diastolic hypertension seems to have an indirect link with intestinal ischemia because of its association with aortic aneurysm [29].

There are several limitations of this study. First, the causes of death from national death records were not verified, but information on the death certificate is known to be reasonably valid in comparison with medical records [30]. Second, the method of BP measurement may have varied among different healthcare centers, leading to measurement error. Third, potential residual confounders such as compliance with antihypertensive medication or other drugs prescribed for the comorbidities of hypertension could not be considered. For antihypertensive medicines, we constructed the variables using drug claim information and included the variables in the multivariate model. As a result, we did not obtain an HR value due to an abnormal proportion of non-users (almost 5%) and rare events from certain diseases. Fourth, this study did not consider the influence of other important factors such as comorbidities of hypertension and compliance on death. Fifth, the possible misclassification of intestinal ischemia (vascular disorder of intestine) should be kept in mind, due to recent changes in

the newly introduced ICD-10, which integrated several diseases into 2 different categories. Sixth, we could not find evidence that the measurement process of BP was standardized, so misclassification error should be considered. The prospective design, relatively large number of participants, sufficient duration of follow-up, completeness of the follow-up data, and the inclusion of ethnically homogeneous participants could be considered as strengths of this study.

Hypertension is a major concern for Korean public health practitioners due to its large disease burden [31,32], but its consequences are usually understood as limited to vascular complications. However, in this study, we investigated associations between BP levels and the risk of death from other specific diseases. We expect that the results of our study will serve as evidence that researchers should include more disease entities when estimating the disease burden of hypertension. Our findings suggest that patients with hypertension are at an elevated risk of death from a variety of additional diseases. These findings show that researchers and public health practitioners may need to track more diseases related to hypertension for patient care, the estimation of disease burden, and policy-making.

In conclusion, Koreans with systolic or diastolic hypertension showed an increased risk of death from DM, ALD, and RF, but a decreased risk of death from interstitial pneumonia. The risk of death from pneumonia and LC was only linked to stage II systolic hypertension. Intestinal ischemia was associated with diastolic hypertension and stage II systolic hypertension. Increased BP seems to increase the risk of death from certain diseases other than cerebrocardiovascular diseases, suggesting that arterial hypertension may affect several organs, in addition to its well-known target organs, although the mechanism remains unclear.

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CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

SUPPLEMENTAL MATERIALS

Supplementary Materials 1-5: Table S1-S5 are available at https://www.jpmph.org/.

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