

Low Systolic Blood Pressure and Mortality From All Causes and Vascular Diseases Among Older Middle-aged Men: Korean Veterans Health Study

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Objectives: Recently, low systolic blood pressure (SBP) was found to be associated with an increased risk of death from vascular diseases in a rural elderly population in Korea. However, evidence on the association between low SBP and vascular diseases is scarce. The aim of this study was to prospectively examine the association between low SBP and mortality from all causes and vascular diseases in older middle-aged Korean men.

Methods: From 2004 to 2010, 94 085 Korean Vietnam War veterans were followed-up for deaths. The adjusted hazard ratios (aHR) were calculated using the Cox proportional hazard model. A stratified analysis was conducted by age at enrollment. SBP was self-reported by a postal survey in 2004.

Results: Among the participants aged 60 and older, the lowest SBP (<90 mmHg) category had an elevated aHR for mortality from all causes (aHR, 1.9; 95% confidence interval [CI], 1.2 to 3.1) and vascular diseases (International Classification of Disease, 10th revision, I00-I99; aHR, 3.2; 95% CI, 1.2 to 8.4) compared to those with an SBP of 100 to 119 mmHg. Those with an SBP below 80 mmHg (aHR, 4.5; 95% CI, 1.1 to 18.8) and those with an SBP of 80 to 89 mmHg (aHR, 3.1; 95% CI, 0.9 to 10.2) also had an increased risk of vascular mortality, compared to those with an SBP of 90 to 119 mmHg. This association was sustained when excluding the first two years of follow-up or preexisting vascular diseases. In men younger than 60 years, the association of low SBP was weaker than that in those aged 60 years or older.

Conclusions: Our findings suggest that low SBP (<90 mmHg) may increase vascular mortality in Korean men aged 60 years or older.

Key words: Blood pressure, Cohort studies, Hypotension, Middle-aged, Mortality, Vascular diseases

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INTRODUCTION

Several studies have suggested that low blood pressure (BP) may be associated with an increased vascular morbidity and mortality, mainly among people with vascular diseases or diabetes [1-8]. However, evidence supporting the association of low systolic blood pressure (SBP) with vascular mortality is scarce in the general population [2,9-11]. In addition, the association between low SBP below 90 to 100 mmHg and vascular mortality has seldom been explored [9,12].

Recently, low SBP was found to be associated with an increased risk of death from vascular diseases in a rural elderly study in the Republic of Korea (hereafter Korea) [12]. We prospectively examined the association between low SBP and mortality from all causes and vascular diseases in the older middle-aged men who are Korean Vietnam War veterans.

METHODS

Study Participants

This study used data from the Korean Veterans Health Study [13,14]. Among the 164 208 veterans who were selected for a postal survey, 117 609 veterans replied (response rate of 71.6%), and their BP, height, and weight were self-reported. Those missing information for SBP ($n=19\ 361$) or body mass index (BMI, $n=3693$) were excluded. In addition, those with self-reported SBP below 60 mmHg ($n=32$) or those with an uncertain residential status after the initial survey ($n=438$) were excluded. Finally, 94 085 men were included in the analysis. This study was approved by the institutional review board of Kwandong University.

Data Collection

The postal survey was mailed on July 27, 2004. Each veteran's age was calculated as of August 1, 2004, which is when the participants were assumed to have received the survey. Information on smoking, alcohol intake, physical activity, BMI, SBP, and income were collected from the survey. The veterans were also asked to indicate all current physician-diagnosed vascular diseases (including hypertension, myocardial infarction, and stroke) as well as any other diseases in the self-reported questionnaire. BMI was calculated from self-reported weight (kg) divided by the square of the height (m). More details about the survey can be obtained elsewhere [13,14].

Follow-up and Outcome Ascertainment

Deaths among subjects from August 1, 2004 through December 31, 2010 were confirmed using the death records held at the National Statistical Office. Follow-up of these death certificates was performed through record linkage at the national level and was completed for all subjects. The main outcomes were death from all causes as well as from vascular diseases (I00-I99), stroke (I60-I64), and ischemic heart diseases (I20-I25) as defined by the International Classification of Disease, 10th revision.

Statistical Analysis

SBP was classified into two versions of seven categories (mmHg; version 1: <90, 90 to 99, 100 to 119 [reference], 120 to 139, 140 to 159, 160 to 179, and ≥ 180 ; version 2: <80, 80 to 89, 90 to 119 [reference], 120 to 139, 140 to 159, 160 to 179, and ≥ 180) [12]. Chi-squared tests and one-way ANOVA were performed to compare differences between SBP categories.

Cox proportional hazard models were used to evaluate the association between baseline SBP and mortality. All analyses were adjusted for the following covariates: age at entry into the study, smoking status, alcohol intake status, physical activity, household income, self-reported prevalence of ischemic heart diseases and stroke, and BMI (kg/m^2 ; <18.5, 18.5-24.9, and ≥ 25). In addition, an age-stratified analysis was performed by dividing subjects into two groups based on age at entry into the study (years; ≥ 60 and <60) to explore whether the association differs by the age group [9,12,15]. Additional analysis was implemented after exclusion of those ($n=1616$) with less than two years of follow-up and those ($n=17\ 376$) with known self-reported stroke and/or ischemic heart diseases. These additional subgroup analyses served as a sensitivity analysis.

Two-sided p -values were calculated, and the statistical significance level was set at 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

During the mean 6.2 years of follow-up (585 587 person-years), 5926 men died, and among them, 961 men died of vascular diseases. The mean (standard deviation) age of the veterans was 58.9 (3.6) years at enrollment. Self-reported prevalence of overweight or obesity ($\text{BMI} \geq 25 \text{ kg}/\text{m}^2$), stroke, ischemic heart diseases, diabetes, and hyperlipidemia had a J-shape association with SBP, while physical activity had a U-shape (or reverse J-shape) association with SBP (Table 1).

Crude all-cause mortality was the lowest in those with an SBP of 120 to 139 mmHg, while crude vascular mortality was the lowest in those with an SBP of 90 to 99 mmHg (Table 2). In the multivariable-adjusted analysis stratified by age group, the lowest SBP category had an increased adjusted hazard ratio (aHR) for all-cause ($p=0.006$) and vascular mortality ($p=0.016$, based on five deaths), among participants aged 60 years or older (Table 2). Except the lowest SBP group, the association between SBP and vascular mortality was similar among age group (Table 2). This J-shape (or U-shape) association between

SBP with mortality, especially vascular disease mortality, in those 60 years or older was maintained when the lowest SBP category was further grouped into two categories (<80 mmHg and 80 to 89 mmHg) and those with an SBP of 90 to 120 mmHg was analyzed as the reference group (Figure 1). The lowest SBP category (<80 mmHg) had a higher risk for stroke (aHR, 7.23; $p=0.065$, based on one death), and ischemic heart diseases mortality (aHR, 6.27; $p=0.078$, based on one death) in men aged 60 or older compared to those with an SBP of 90 to 119 mmHg.

Compared to those with an SBP of 90 to 119 mmHg, the association in the lowest SBP (<80 mmHg) was sustained after

additional adjustment for known prevalent hypertension, diabetes, and hyperlipidemia (aHR, 4.45; 95% CI, 1.06 to 18.8) among those aged 60 or older. In men aged 60 or older, the results associated with the lowest SBP category (<80 mmHg) compared to the 90 to 119 mmHg SBP category did not differ from the main analysis when the analyses were done among survivors as of August 1, 2006 (aHR, 5.81; 95% CI, 1.36 to 24.9) or those with no known ischemic heart disease (aHR, 3.97; 95% CI, 0.52 to 30.6). When we analyzed data among the elderly aged 65 years or older ($n=6038$), the lowest SBP (<80 mmHg) had a stronger association with vascular mortality (aHR, 5.31; 95% CI, 0.67 to 42.3) than that observed in the main analysis, with the

Table 1. Characteristics of the older middle-aged Korean men by SBP group

Variables	SBP (mmHg)								p-value ¹
	Total (n=94 085)	<90 (n=317)	90-99 (n=1019)	100-119 (n=8056)	120-139 (n=36 570)	140-159 (n=27 446)	160-179 (n=13 629)	≥180 (n=7048)	
Age (y)	58.9±3.6	59.1±4.0	58.8±3.4	58.8±3.5	58.9±3.7	59.1±3.8	58.9±3.4	58.8±3.2	<0.001 ²
BMI (kg/m ²)	23.8±2.6	22.3±2.9	22.2±2.8	22.7±2.6	23.6±2.6	24.1±2.6	24.2±2.7	24.1±2.7	<0.001 ²
SBP (mmHg)	139.5±22.5	78.5±6.6	91.5±2.7	108.4±4.7	125.9±5.5	144.6±5.3	164.0±5.0	188.2±14.8	<0.001 ²
Smoking									
Current smoker	32 477 (34.5)	95 (30.0)	346 (34.0)	2810 (34.9)	13 006 (35.6)	9253 (33.7)	4570 (33.5)	2397 (34.0)	<0.001
Past smoker	44 086 (46.9)	161 (50.8)	460 (45.1)	3711 (46.1)	17 083 (46.7)	13 089 (47.7)	6412 (47.0)	3170 (45.0)	
Never smoker	17 522 (18.6)	61 (19.2)	213 (20.9)	1535 (19.1)	6481 (17.7)	5104 (18.6)	2647 (19.4)	1481 (21.0)	
Alcohol intake									
≥5 times/wk	9603 (10.2)	31 (9.8)	62 (6.1)	640 (7.9)	3772 (10.3)	3052 (11.1)	1374 (10.1)	672 (9.5)	<0.001
1-4 times/wk	36 365 (38.7)	75 (23.7)	266 (26.1)	2637 (32.7)	14 183 (38.8)	11 304 (41.2)	5407 (39.7)	2493 (35.4)	
<1 time/wk	34 351 (36.5)	113 (35.6)	421 (41.3)	3255 (40.4)	13 441 (36.8)	9654 (35.2)	4855 (35.6)	2612 (37.1)	
Non-drinker	13 766 (14.6)	98 (30.9)	270 (26.5)	1524 (18.9)	5174 (14.1)	3436 (12.5)	1993 (14.6)	1271 (18.0)	
Physical activity									
Yes	29 530 (31.4)	125 (39.4)	417 (40.9)	2628 (32.6)	11 044 (30.2)	8275 (30.2)	4461 (32.7)	2580 (36.6)	
BMI (kg/m ²)									
<18.5	2136 (2.3)	33 (10.4)	95 (9.3)	392 (4.9)	840 (2.3)	401 (1.5)	226 (1.7)	149 (2.1)	<0.001
18.5-24.9	63 274 (67.3)	229 (72.2)	773 (75.9)	6255 (77.6)	25 789 (70.5)	17 528 (63.9)	8359 (61.3)	4341 (61.6)	
≥25	28 675 (30.5)	55 (17.4)	151 (14.8)	1409 (17.5)	9941 (27.2)	9517 (34.7)	5044 (37.0)	2558 (36.3)	
Household income (Korean won)									
<500 000	11 010 (11.7)	79 (24.9)	161 (15.8)	887 (11.0)	3623 (9.9)	2944 (10.7)	1998 (14.7)	1318 (18.7)	<0.001
500 000-990 000	18 563 (19.7)	83 (26.2)	231 (22.7)	1484 (18.4)	6215 (17.0)	5380 (19.6)	3293 (24.2)	1877 (26.6)	
1 000 000-1 490 000	22 597 (24.0)	70 (22.1)	231 (22.7)	1895 (23.5)	8417 (23.0)	6752 (24.6)	3449 (25.3)	1783 (25.3)	
≥1 500 000	41 915 (44.6)	85 (26.8)	396 (38.9)	3790 (47.0)	18 315 (50.1)	12 370 (45.1)	4889 (35.9)	2070 (29.4)	
Prevalent self-reported diseases									
Ischemic heart diseases	13 642 (14.5)	56 (17.7)	155 (15.2)	1002 (12.4)	3820 (10.4)	4213 (15.4)	2734 (20.1)	1662 (23.6)	<0.001
Stroke	5148 (5.5)	17 (5.4)	35 (3.4)	289 (3.6)	1431 (3.9)	1755 (6.4)	1006 (7.4)	615 (8.7)	<0.001
Diabetes	20 355 (21.6)	60 (18.9)	142 (13.9)	1158 (14.4)	5990 (16.4)	6627 (24.1)	3922 (28.8)	2456 (34.8)	<0.001
Hyperlipidemia	16 126 (17.1)	39 (12.3)	105 (10.3)	907 (11.3)	4565 (12.5)	5423 (19.8)	3288 (24.1)	1799 (25.5)	<0.001

Values are presented as mean ± standard deviation or number (%).

SBP, systolic blood pressure; BMI, body mass index.

¹Chi-squared test between SBP groups.

²One-way ANOVA between SBP groups.

Table 2. Numbers of deaths and adjusted¹ HR for mortality by age group among older middle-aged Korean men during 2004-2010

Age (y)	SBP (mmHg)	All-cause mortality					Vascular mortality (I00-I99) ²				
		No. of deaths	Crude rate ³	p-value	HR	95% CI	No. of deaths	Crude rate ³	p-value	HR	95% CI
Total	<90	35	1830	0.14	1.29	0.92, 1.82	7	366	0.04	2.23	1.02, 4.89
	90-99	97	1563	0.03	1.28	1.03, 1.59	7	113	0.68	0.85	0.39, 1.86
	100-119	523	1048		1.00	Reference	59	118		1.00	Reference
	120-139	2178	956	0.96	1.00	0.91, 1.10	304	133	0.12	1.25	0.94, 1.65
	140-159	1647	962	0.89	0.99	0.90, 1.10	313	183	0.003	1.53	1.16, 2.03
	160-179	878	1034	0.62	1.03	0.92, 1.15	150	177	0.04	1.38	1.02, 1.87
	≥180	568	1305	0.002	1.21	1.07, 1.37	121	278	<0.001	1.93	1.41, 2.65
≥60	<90	19	3476	0.006	1.93	1.20, 3.10	5	915	0.02	3.24	1.24, 8.42
	90-99	32	1846	0.33	1.21	0.83, 1.75	1	58	0.23	0.29	0.04, 2.14
	100-119	187	1408		1.00	Reference	27	203		1.00	Reference
	120-139	842	1353	0.41	1.07	0.91, 1.25	150	241	0.15	1.35	0.89, 2.04
	140-159	679	1323	0.79	1.02	0.87, 1.20	129	251	0.27	1.27	0.83, 1.92
	160-179	347	1474	0.30	1.10	0.92, 1.31	61	259	0.40	1.22	0.77, 1.92
	≥180	220	1847	0.01	1.30	1.07, 1.58	55	462	0.006	1.93	1.21, 3.07
<60	<90	16	1171	0.71	0.91	0.55, 1.50	2	146	0.81	1.19	0.28, 4.98
	90-99	65	1453	0.04	1.32	1.01, 1.73	6	134	0.60	1.26	0.53, 3.02
	100-119	336	917		1.00	Reference	32	87		1.00	Reference
	120-139	1336	806	0.59	0.97	0.86, 1.09	154	93	0.42	1.17	0.80, 1.71
	140-159	968	808	0.78	0.98	0.87, 1.11	184	154	0.002	1.80	1.23, 2.62
	160-179	531	865	0.89	0.99	0.86, 1.14	89	145	0.04	1.52	1.01, 2.29
	≥180	348	1100	0.04	1.17	1.01, 1.36	66	209	0.002	1.95	1.28, 2.99

SBP, systolic blood pressure; CI, confidence interval; HR, hazard ratio.

¹Age at study entry, smoking status, alcohol intake status, physical activity, household income, prevalent self-reported ischemic heart diseases, prevalent self-reported stroke, and body mass index.

²Vascular diseases (I00-I99) was defined by the International Classification of Disease, 10th revision.

³Crude death rate per 100 000 person-years.

90 to 119 mmHg SBP category as the reference group.

DISCUSSION

This study found that a self-reported SBP below 90 mmHg was associated with an increased risk of mortality and vascular mortality. In addition, our results suggest that the association of self-reported SBP with mortality from vascular diseases may be a J-curve in men aged 60 years or older.

Since the self-reported prevalence of overweight or obesity (BMI ≥ 25 kg/m²), stroke, ischemic heart diseases, diabetes, and hyperlipidemia had a J-shape association with SBP, the potential reverse causation (that is, the suggestion that low SBP could be an epiphenomenon related to concurrent chronic diseases related to subsequent death) was evaluated [11,12,16]. The J-shape associations with all-cause and vascular mortality were maintained after adjustment for BMI and the preexisting-

diseases (including hypertension, ischemic heart diseases, stroke, diabetes, and hyperlipidemia). After excluding the early follow-up data, the J-shape association with vascular mortality in men aged 60 or older was not changed. When men with preexisting vascular diseases were dropped from the analysis, the J-shape association was sustained, although the statistical association was weakened due to the small number of deaths. Additionally, the lowest SBP was not linked with cancer mortality, in the current study. Nonetheless, reverse causation cannot be ruled out in the present study.

The low SBP has seldom been associated with vascular diseases in prospective studies among the general population [10-12]. Having an SBP of 90 to 99 mmHg was not associated with an increased risk of vascular mortality in men aged 60 or older, and these results are different than those from a previous study on a Korean rural elderly population [12]. However, when the analysis was restricted to men aged 65 or older, an SBP of 90 to

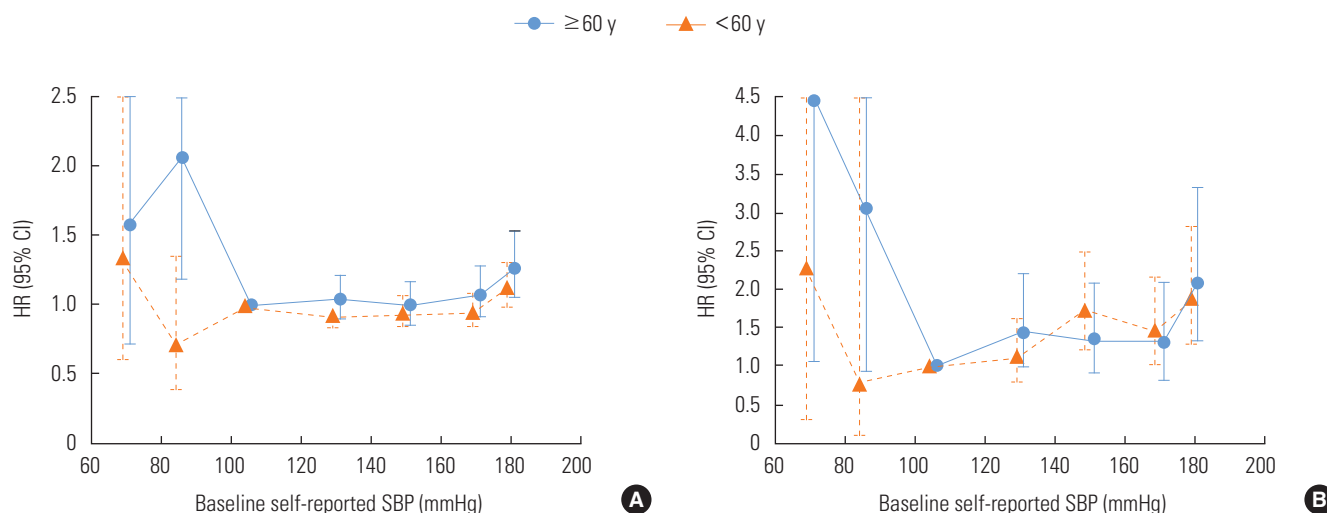


Figure 1. Multivariable-adjusted¹ HR for mortality according to age group during 2004-2010 across the seven categories of SBP (mmHg; <80, 80-89, 90-119 [reference], 120-139, 140-159, 160-179, and ≥180). The midpoint SBP was used as the representative value for each category, except for the lowest (70 mmHg) and the highest (180 mmHg) SBP categories where the median was used as the representative value. (A) Deaths from all-cause, (B) death from vascular diseases. Death from vascular diseases (I00-I99) was defined by the International Classification of Disease, 10th revision. SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval. ¹Adjusted for age at entry, smoking status, alcohol intake status, physical activity, income status, self-reported ischemic heart diseases, self-reported stroke, and body mass index.

99 mmHg was associated with a modestly high risk of vascular mortality (aHR, 1.32; $p=0.796$) in accordance with the previous research.

The prospective design and complete follow-up constitute the principle strengths of our study. However, there are also several limitations. First, it is a limitation that BP was self-reported; however, the finding that vascular mortality increased in conjunction with an increasing trend in self-reported SBP indicates that self-reported BP in the present study could have reasonable validity, which is in accordance with other research [17]. Second, due to the small number of deaths in the lowest SBP category, the statistical power may have been decreased, and the elevated mortality in the lowest SBP category might have resulted from chance alone [12]. Third, the diagnoses of the death certificates were not validated separately. Since any misclassification of the diagnoses of death could most likely be non-differential according to SBP, potential misclassifications would not be expected to substantially overestimate the hazard ratios. Fourth, our study participants were Vietnam War veterans who have a lower mortality than that expected in the general population [18], and they had smaller BMIs than those in European-origin populations do. Thus, some of our results may not be generalizable to other populations [19].

In Korean men aged 60 and above, having an SBP below 90

mmHg may increase death from vascular diseases. Further research is needed to confirm this association in other populations and, if the association exists, the underlying mechanism.

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CONFLICT OF INTEREST

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

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