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High normotension is associated with future metabolic syndrome but not cardiovascular disease

A 10-year longitudinal study

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Abstract

Hypertension and prehypertension can increase the risk of developing cardiovascular disease (CVD) and diabetes. However, whether the harmful effects of high blood pressure (BP) are also seen with high normotension remains unknown. This 10-year longitudinal follow-up study aimed to investigate the relationships among normal-range BP, metabolic syndrome (MetS), and CVD.

A total of 9133 nonmedicated normotensive participants, 4634 males and 4499 females, aged 60 years or older were enrolled in a standard health examination program at 2 academic hospitals and a health screening center in Taiwan. The study subjects were divided into 3 groups according to their BP. The systolic BP (SBP) ranges of groups 1, 2, and 3 were 91 to 100, 101 to 110, and 111 to 119 mmHg, whereas the diastolic BP (DBP) ranges of groups 1, 2, and 3 were 51 to 60, 61 to 70, and 71 to 79 mmHg, respectively.

In the SBP3 group, both sexes had a higher odds ratio (OR) for having MetS or abnormal MetS components, except for triglycerides. Females in the DBP3 group had a higher OR for having MetS at baseline. After the follow-up period, the SBP3 group had a significantly higher hazard ratio (HR) for developing MetS. Males in the DBP3 group and females in the DBP2 and DBP3 groups had a significantly higher HR for developing MetS. Neither the SBP3 group nor the DBP3 group had a higher HR for developing nonfatal CVD. In the Kaplan-Meier analysis, SBP and DBP in both sexes showed statistical significance as predictors of MetS, but not of nonfatal CVD.

High normotensive elderly individuals have an elevated risk of developing MetS at baseline and within 10 years of follow-up, but they are not at increased risk of CVD. Preventive interventions, such as life-style modification, should be offered early even to the apparently healthy elderly.

Abbreviations: BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL-C = High-density lipoprotein cholesterol, HR = hazard ratio, LDL-C = Low-density lipoprotein cholesterol, MetS = metabolic syndrome, OR = odds ratio, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, WC = waist circumference, WHO = World Health Organization.

Keywords: cardiovascular disease, metabolic syndrome, normotension, preventive geriatrics, primary prevention

1. Introduction

The high prevalence of cardiovascular disease (CVD) has created a serious health burden in the world today. The results of several large cohorts, including the Framingham Heart Study, demonstrated that hypertension is an independent risk factor of future CVD.[1] Additionally, hypertension is known to be associated with not only insulin resistance but also type 2 diabetes

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mellitus.[2,3] Moreover, strong evidence has manifested that subjects with prehypertension are still at higher risk for CVD and type 2 diabetes mellitus.[4–10] However, whether the harmful effects of high blood pressure (BP) extend to high normotension (systolic BP [SBP] <120 mmHg and diastolic BP [DBP] <80 mmHg)[11] remains unknown, and is of clinical interest.

The term "metabolic syndrome" (MetS), defined as the cluster of central obesity, hypertension, glucose intolerance, and dyslipidemia, was first proposed by the World Health Organization (WHO) in 1998.[12] Evidence has shown that MetS is associated with insulin resistance and the future development of CVD.[13] In adults, the estimated prevalence of MetS is 23.7% in the United States and 15.7% in Taiwan.[14,15] One systematic review and meta-analysis study concluded that lowering SBP to normotensive range should be routinely considered for the prevention of CVD among those deemed to be of sufficient absolute risk.[16] It is noteworthy that individuals at baseline had a history of major diseases, such as coronary heart disease, stroke, diabetes, heart failure, and chronic kidney disease. Our group previously conducted several cross-sectional studies for nonmedicated healthy adult and elderly individuals, and reported that subjects with higher normotensive SBP have higher chances of having MetS.[17–19] However, determining what is the suitable BP range is a difficult question for elderly individuals with SBP and DBP at the high end of the normal range. All of the previous studies had no definite cutoff value for the SBP, which makes their utility value in clinical practice low. Furthermore, we did not evaluate DBP and a combined SBP and DBP analysis, which is an important limitation of the previous studies, as it is believed that both SBP and DBP influence subjects' health. Nevertheless, there is less focus on DBP in the current literature. To further investigate this unknown area, it is important to understand how different ranges of normotension impact MetS and CVD.

This 10-year longitudinal follow-up study aimed to investigate the relationship between different baseline levels of BP within the normal range and the future development of MetS or nonfatal CVD.

2. Methods

2.1. Study participants

This study enrolled subjects aged 60 years or older in a standard health examination program at Tri-Service General Hospital (TSGH), Cardinal Tien Hospital (CTH), and the MJ Health Management Institution from January 1999 to December 2015. TSGH is a north Taiwan medical center. CTH is a north Taiwan district hospital. MJ Health Management Institution is a large health screening center in Taiwan and has provided health screening services for over 1 million persons. Written informed consent was obtained from all participants, and the study protocol was approved by the institutional review board of the institutions. Data were recorded in anonymous form and information related to the identification of individuals was removed.

A total of 19,565 subjects had visits arranged on an annual basis and were followed up for 10 years from the day of entry to observe whether they developed MetS or nonfatal CVD during this period. Questionnaires were used to capture data regarding diabetes, antidiabetic therapy (diet, oral, or insulin medication), use of antihypertensive, lipid-lowering, or antithrombotic drugs, stroke (ischemic or hemorrhagic), or cardiac event (defined as unstable angina or angina pectoris, myocardial infarction, procedures such as percutaneous transluminal coronary angioplasty or bypass surgery) annually. Nonfatal CVD outcome measures included the combination of nonfatal stroke and nonfatal cardiac events. Lifestyle was evaluated by the strength intensity of work type, frequency and intensity of participation in sports, level of alcohol consumption, and smoking status. All the variables were semiquantitative by 5 scales (from none to heaviest). At baseline, those with a history of major medical diseases, and those receiving medications for hypertension, diabetes, hyperlipidemia, or other medications known to affect blood glucose, lipids, or BP, were excluded. We also excluded subjects taking any medication that could affect the components of MetS. This was to observe the real association between BP and other related physiological and pathological effects. In other words, we included subjects with newly diagnosed MetS and other relative healthy elderly participants without MetS. The observations were conducted at baseline and subjects with MetS at baseline were excluded during the follow-up observation. In the follow-up period, we included subjects who were taking medications for hypertension, diabetes, and dyslipidemia. All the patients were asked to receive annual health check-ups throughout the follow-up period. However, some patients were lost to follow-up without a second visit, and we excluded those subjects. During the follow-up period, the aforementioned examinations, including questionnaires, physical examinations, and blood tests, were performed.

We excluded subjects as follows:

1. 473 subjects with missing data regarding components of MetS at baseline.
2. 4558 subjects with a history of hypertension, diabetes, or hyperlipidemia, or taking medications for these diseases at baseline.
3. 2361 subjects with other related comorbidities such as minor cardiovascular events (stable or unstable angina or minor stroke) at baseline.
4. 1894 subjects with BP ≥120/80 mmHg or ≤90/50 mmHg at baseline.
5. 1146 subjects with visits occurring less than twice during the 10-year follow-up period.

This resulted in a total of 9133 subjects who were eligible for analysis at baseline. To observe the relationships between BP and the MetS components, we analyzed the data separately according to SBP and DBP. We further divided the study subjects into 3 groups according to their BP measurements (10 mmHg ranges) as follows: the ranges of SBP groups 1, 2, and 3 were 91 to 100, 101 to 110, and 111 to 119 mmHg, whereas the DBP ranges of group 1, 2, and 3 were 51 to 60, 61 to 70, and 71 to 79 mmHg, respectively. In the follow-up analysis, 2189 subjects with MetS at baseline were excluded. We excluded subjects with MetS, but not subjects with any abnormal MetS components. The number of subjects enrolled in follow-up analysis was 9133 minus 2189, and equals 6944. The development of future MetS and nonfatal CVD among the 3 groups was assessed.

2.2. Anthropometric and laboratory data

Participants visited the clinic at 8 AM after at least a 10-hour fast. Information about medical history, lifestyle, alcohol intake, smoking, and physical exercise was obtained through an interview with a well-trained senior nursing-staff member, and was recorded in a questionnaire. Complete physical examinations were conducted. All participants were measured wearing

light clothing and no shoes. Body mass index (BMI) was calculated as the weight (kiligrams) divided by the square of the height (meters) (kiligram per square meters). Waist circumference (WC) (centimeters) was measured in a horizontal plane at a level midway between the inferior margin of the last rib and the crest of the ilium. The nursing staff used mercury sphygmomanometers to measure SBP and DBP, with suitably sized cuffs on the right arms of the participants. All participants were seated after at least 5 minutes of rest and measurements were repeated twice >1-minute apart. The average value was recorded and included in the analysis. The measurements of BP conformed to the recommendations of the American Heart Association.[20]

After a 10-hour overnight fast, blood samples were collected from each participant and plasma samples were separated within 1 hour and stored at −70 °C. Fasting plasma glucose (FPG) and lipid concentrations were evaluated. FPG was measured by using glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Spring Instruments, Yellow Spring, OH). The dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan) was used to determine total cholesterol (TC) and triglycerides (TG) values. Serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) profiles were determined by using an enzymatic cholesterol assay, following dextran sulfate precipitation.

2.3. Definition and classification of BP level

The BP level classification in the present study was according to the recommendation of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[11] The ranges of SBP/DBP for hypertension, prehypertension, normotension, and high normotensive are as follows: >140/90, 120 to 139/80 to 89, <120/80, and 111 to 119/71 to 79 mmHg, respectively. Only subjects with normotension at baseline were enrolled in the present study.

2.4. Definition of metabolic syndrome and nonfatal CVD

The participants were evaluated for MetS using the latest harmonized criteria in 2009.[21] MetS is clinically defined by the presence of ≥3 of the following: central obesity (WC ≥90 cm in men, ≥80 cm in women, for Asians), elevated TG values (≥150 mg/dL), reduced HDL-C values (<40 mg/dL for men, <50 mg/dL for women), elevated BP (SBP ≥130 mmHg or DBP ≥85 mmHg), and elevated FPG concentration (≥100 mg/dL).

The outcome of nonfatal CVD in the present study was defined as a group of disorders of the heart and blood vessels, based on the definition provided by the WHO: coronary heart disease, cerebrovascular disease, peripheral arterial disease, deep vein thrombosis, and pulmonary embolism.[22]

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 24.0 (IBM, Somers, NY). All data were tested for normal distribution using the Kolmogorov–Smirnov test and for homogeneity of variances using Levene test. Continuous variables were expressed as means ± standard deviation. One-way analysis of variance test was used to evaluate the differences between the 3 groups. The Bonferroni test was applied for post hoc comparisons. Multivariate logistic regression analysis was carried out to calculate the odds ratios (OR) for an increased risk of having MetS and each abnormal MetS component among the 3 groups at baseline. The association of the different BP groups with the development of future MetS and nonfatal CVD was determined using Cox proportional hazard regression. Kaplan-Meier analysis with a log-rank test was applied to determine event-free probabilities. All statistical tests were 2-sided and a value of $P < .05$ was considered to be statistically significant.

3. Results

The clinical characteristics of the study participants are shown in Table 1. Among the 3 SBP groups, subjects with SBP3 were older and had higher levels of BMI, WC, SBP, DBP, TC, and TG in both sexes. FPG and LDL-C were higher in SBP3 only in female participants. Although there was a trend toward lower HDL-C levels in females, it did not reach statistical significance. Similarly, age, BMI, WC, SBP, DBP, and TG were all higher in the DBP3 group in both sexes. Also in the DBP3 group, TC and LDL-C were higher only in males, whereas HDL-C was lower only in females. Interestingly, FPG was lower in this group with statistical significance in males and a trend in females.

In multivariate logistic regression analysis at baseline (Table 2), both sexes in the SBP3 group had a greater risk of having MetS or abnormal MetS components, except for TG. Males with DBP3 had a greater risk of abnormal WC and HDL-C, and females had a greater risk of abnormal WC, HDL-C, TG, and MetS. During the follow-up period (Table 3), only males in the SBP3 group had a statistically significant hazard ratio (HR) for developing MetS (1.882, 95% confidence interval [CI] 1.123–3.156). Males in the DBP3 group and females in the DBP2 and DBP3 groups had a significant HR for predicting MetS. Neither the SBP3 nor DBP3 groups had a statistically significant HR for developing future nonfatal CVD.

Finally, in the Kaplan-Meier plot (Fig. 1), for both sexes, SBP and DBP measurements were statistically significant predictors of MetS, but not of nonfatal CVD. Both sexes in the SBP3 group had a lower rate of event-free probability for MetS ($P = .019$ and .001 in males and females, respectively). Both sexes in the DBP1 group had a higher rate of event-free probability for MetS ($P = .001$ and .002 in males and females, respectively).

4. Discussion

Higher normotension involving either SBP or DBP is associated with a higher risk of developing future MetS, but not CVD, in both sexes. The present study raises some interesting questions about the role of BP, even when it is still within its normal range. In addition, a lower threshold for developing future MetS was noted in females, which suggests the possibility of different sex-related BP control levels in the elderly.

The association between central obesity and an increased risk of prehypertension in Chinese, whites, blacks, and Hispanics is well documented.[23,24] Moreover, the positive relationship between SBP and adiposity has been clearly demonstrated in many different studies.[25] Tsai et al[26] found that, among 1186 female Taiwanese participants, 37.4% of prehypertensives were obese compared with 21.4% of normotensives. Other studies found similar results in 4400 Israeli and 7637 Chinese women.[6,24] The present results were consistent with those of these studies, showing that the effect of BMI and WC on BP is strong and could be extended downward when BP is in the normal range.

Table 1

Clinical characteristics of the study subjects at baseline in males and females classified according to blood pressure.

(A) Systolic blood pressure subgroups

	SBP1	SBP2	SBP3
Males			
N	460	1579	2595
Age, y	64.5±4.9	64.6±5.2	65.1±5.4*,†
BMI, kg/m^2	22.4±2.9	22.8±3.0*	23.3±2.9*,†
WC, cm	80.9±8.6	82.0±8.8*	83.2±8.4*,†
SBP, mmHg	95.5±2.9	105.1±2.8*	114.7±2.9*,†
DBP, mmHg	61.0±6.3	65.0±6.0*	68.3±6.0*,†
FPG, mg/dL	105.1±34.0	105.7±31.9	106.2±28.6
TC, mg/dL	192.0±35.3	196.9±36.0*	197.8±36.8*
HDL-C, mg/dL	50.5±14.8	51.3±14.7	50.2±13.7†
LDL-C, mg/dL	119.9±31.3	123.1±31.5	123.4±33.5
TG, mg/dL	108.3±57.9	112.7±60.8	120.0±63.8*,†
Females			
N	479	1466	2554
Age, y	62.4±3.5	63.4±4.2*	63.8±4.3*,†
BMI, kg/m^2	22.5±3.0	23.0±3.1*	23.5±3.1*,†
WC, cm	73.7±7.0	75.5±7.7*	76.6±8.0*,†
SBP, mmHg	95.3±2.9	105.0±2.9*	114.8±2.9*,†
DBP, mmHg	58.9±6.0	62.6±6.2*	66.2±6.0*,†
FPG, mg/dL	101.8±23.7	102.7±27.2	105.0±28.6†
TC, mg/dL	205.4±34.8	208.3±36.8	212.0±37.4*,†
HDL-C, mg/dL	61.0±16.1	60.4±16.0	59.9±15.9
LDL-C, mg/dL	123.1±31.5	124.9±33.6	127.9±34.1*,†
TG, mg/dL	106.2±54.0	114.6±58.1*	121.1±71.5*,†

(B) Diastolic blood pressure subgroups

	DBP1	DBP2	DBP3
Males			
N	687	2345	1602
Age, y	66.6±6.3	65.0±5.2*	63.9±4.6*,†
BMI, kg/m^2	22.4±3.0	22.9±2.8*	23.5±3.0*,†
WC, cm	81.2±9.0	82.1±8.5*	83.7±8.6*,†
SBP, mmHg	103.7±8.7	108.8±7.0*	112.3±5.7*,†
DBP, mmHg	55.9±2.7	64.8±2.8*	73.3±2.6*,†
FPG, mg/dL	109.7±42.6	105.5±28.4*	104.7±26.1*
TC, mg/dL	191.4±37.1	196.2±36.7*	200.3±35.3*,†
HDL-C, mg/dL	50.1±14.3	50.8±14.1	50.5±14.2
LDL-C, mg/dL	119.2±32.5	122.7±32.5*	124.9±32.6*
TG, mg/dL	110.4±61.8	113.5±60.4	122.3±64.5*,†
Females			
N	1051	2427	1021
Age, y	64.0±4.7	63.4±4.1*	63.2±3.9*
BMI, kg/m^2	22.7±3.0	23.3±3.1*	23.7±3.2*,†
WC, cm	74.8±7.3	75.9±7.9*	77.1±8.2*,†
SBP, mmHg	104.8±8.2	109.9±7.0*	112.7±5.7*,†
DBP, mmHg	55.7±2.6	64.2±2.8*	73.1±2.6*,†
FPG, mg/dL	104.5±27.1	103.9±28.7	103.2±25.2
TC, mg/dL	209.3±37.4	210.2±36.7	211.1±37.3
HDL-C, mg/dL	61.4±16.2	60.0±15.8*	59.5±16.2*
LDL-C, mg/dL	126.0±34.5	126.7±33.3	126.3±33.8
TG, mg/dL	109.6±56.5	117.2±60.5*	125.6±83.1*,†

Data are shown as mean±standard deviation. BMI=body mass index, DBP=diastolic blood pressure, FPG=fasting plasma glucose, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, N=number, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, WC=waist circumference.

* $P<.05$ against DBP1.

† $P<.05$ against DBP2.

Higher BP is associated with a higher risk of developing type 2 diabetes mellitus. This phenomenon is seen not only in patients with hypertension, but also in subjects with prehypertension.[27] The underlying pathogenesis of insulin resistance in hypertensive patients is postulated to be related to increased renal tubular sodium reabsorption, increased sympathetic nervous system activity, and increased arterial wall smooth muscle reactivity.[28] Although the present study found that a high-normal SBP was associated with a risk of higher FPG, this relationship was not highly correlated with DBP and FPG. The pathophysiology of age-associated increases in arterial stiffness causes SBP to increase and DBP to decrease.[29] This lowering of DBP in the elderly may

Table 2

Odds ratios for having metabolic syndrome and each abnormal component in males and females in relation to blood pressure groups at baseline.

(A) Systolic blood pressure subgroups

		SBP1	SBP2	SBP3
Males				
WC ≥90 cm	OR	Ref.	1.229 (0.930–1.623)	1.468 (1.126–1.915)
	P	—	.148	.005
FPG ≥100 mg/dL	OR	Ref.	0.997 (0.809–1.229)	1.319 (1.080–1.609)
	P	—	.979	.007
HDL-C <40 mg/dL	OR	Ref.	1.165 (0.888–1.528)	1.517 (1.172–1.961)
	P	—	.270	.002
TG ≥150 mg/dL	OR	Ref.	0.968 (0.755–1.241)	0.979 (0.772–1.241)
	P	—	.796	.859
Metabolic syndrome	OR	Ref.	1.136 (0.792–1.629)	1.510 (1.074–2.122)
	P	—	.487	.018
Females				
WC ≥80 cm	OR	Ref.	1.674 (1.290–2.172)	2.142 (1.672–2.744)
	P	—	<.001	<.001
FPG ≥100 mg/dL	OR	Ref.	1.105 (0.894–1.366)	1.371 (1.122–1.675)
	P	—	.354	.002
HDL-C <50 mg/dL	OR	Ref.	1.435 (1.091–1.886)	1.699 (1.310–2.203)
	P	—	.010	<.001
TG ≥150 mg/dL	OR	Ref.	1.101 (0.865–1.400)	1.240 (0.988–1.557)
	P	—	.436	.064
Metabolic syndrome	OR	Ref.	1.658 (1.165–2.362)	1.996 (1.424–2.796)
	P	—	.005	<.001

(B) Diastolic blood pressure subgroups

		DBP1	DBP2	DBP3
Males				
WC ≥90 cm	OR	Ref.	1.176 (0.936–1.479)	1.751 (1.387–2.211)
	P	—	.165	<.001
FPG ≥100 mg/dL	OR	Ref.	0.980 (0.827–1.161)	1.024 (0.857–1.225)
	P	—	.812	.793
HDL-C <40 mg/dL	OR	Ref.	1.205 (0.969–1.498)	1.496 (1.195–1.873)
	P	—	.094	<.001
TG ≥150 mg/dL	OR	Ref.	0.881 (0.721–1.077)	0.912 (0.738–1.126)
	P	—	.215	.392
Metabolic syndrome	OR	Ref.	1.018 (0.772–1.343)	1.274 (0.959–1.693)
	P	—	.897	.095
Females				
WC ≥80 cm	OR	Ref.	1.406 (1.187–1.665)	1.837 (1.514–2.230)
	P	—	<.001	<.001
FPG ≥100 mg/dL	OR	Ref.	0.952 (0.823–1.102)	0.910 (0.765–1.082)
	P	—	.512	.286
HDL-C <50 mg/dL	OR	Ref.	1.244 (1.038–1.491)	1.556 (1.265–1.914)
	P	—	.018	<.001
TG ≥150 mg/dL	OR	Ref.	1.155 (0.977–1.366)	1.312 (1.080–1.594)
	P	—	.091	.006
Metabolic syndrome	OR	Ref.	1.315 (1.052–1.644)	1.706 (1.328–2.191)
	P	—	.016	<.001

(C) Combined systolic and diastolic blood pressure subgroups

		BP1	BP2	BP3
Males				
WC ≥90 cm	OR	Ref.	1.184 (0.987–1.419)	1.532 (1.285–1.826)
	P	—	.069	<.001
FPG ≥100 mg/dL	OR	Ref.	1.193 (1.036–1.373)	1.401 (1.217–1.614)
	P	—	.014	<.001
HDL-C <40 mg/dL	OR	Ref.	1.091 (0.923–1.291)	0.972 (0.820–1.153)
	P	—	.308	.746
TG ≥150 mg/dL	OR	Ref.	1.408 (1.181–1.679)	1.553 (1.305–1.848)
	P	—	<.001	<.001
Metabolic syndrome	OR	Ref.	1.344 (1.068–1.691)	1.489 (1.187–1.867)

(*continued*)

Table 2

(continued).

(C) Combined systolic and diastolic blood pressure subgroups

		BP1	BP2	BP3
	P	—	.012	.001
Females				
WC ≥80 cm	OR	Ref.	1.288 (1.095–1.516)	1.669 (1.423–1.957)
	P	—	.002	<.001
FPG ≥100 mg/dL	OR	Ref.	1.184 (1.025–1.368)	1.269 (1.099–1.467)
	P	—	.022	.001
HDL-C <50 mg/dL	OR	Ref.	1.143 (0.972–1.345)	1.201 (1.021–1.411)
	P	—	.107	.027
TG ≥150 mg/dL	OR	Ref.	1.284 (1.079–1.527)	1.348 (1.135–1.603)
	P	—	.005	.001
Metabolic syndrome	OR	Ref.	1.340 (1.086–1.653)	1.410 (1.145–1.737)
	P	—	.006	.001

BP = combined systolic and diastolic blood pressure subgroups, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein-cholesterol, OR = odds ratio, Ref = reference, SBP = systolic blood pressure, TG = triglycerides, WC = waist circumference. Odds ratio was adjusted for age, body mass index, and life style including work, sports, alcohol consumption, and smoking.

Table 3

Hazard ratios for predicting metabolic syndrome and nonfatal cardiovascular disease in males and females at follow-up.

(A) Systolic blood pressure group

		SBP1	SBP2	SBP3
Males				
Metabolic syndrome	HR	Ref.	1.353 (0.789–2.322)	1.882 (1.123–3.156)
	P	—	.272	.016
Nonfatal cardiovascular disease	HR	Ref.	1.616 (0.623–4.190)	1.989 (0.791–5.001)
	P	—	.324	.144
Females				
Metabolic syndrome	HR	Ref.	0.924 (0.584–1.461)	1.493 (0.983–2.269)
	P	—	.735	.060
Nonfatal cardiovascular disease	HR	Ref.	0.916 (0.385–2.180)	1.245 (0.559–2.772)
	P	—	0.843	.591

(B) Diastolic blood pressure group

		DBP1	DBP2	DBP3
Males				
Metabolic syndrome	HR	Ref.	1.565 (0.992–2.469)	1.891 (1.192–3.000)
	P	—	.054	.007
Nonfatal cardiovascular disease	HR	Ref.	1.119 (0.575–2.180)	1.119 (0.560–2.237)
	P	—	.740	.751
Females				
Metabolic syndrome	HR	Ref.	1.463 (1.031–2.078)	1.827 (1.246–2.680)
	P	—	.033	.002
Nonfatal cardiovascular disease	HR	Ref.	0.995 (0.540–1.832)	1.023 (0.499–2.097)
	P	—	.987	.951

(C) Combined systolic and diastolic blood pressure subgroups

		BP1	BP2	BP3
Males				
Metabolic syndrome	HR	Ref.	1.673 (1.205–2.321)	1.802 (1.301–2.495)
	P	—	.002	<.001
Nonfatal cardiovascular disease	HR	Ref.	0.993 (0.587–1.680)	0.768 (0.641–1.826)
	P	—	.979	.768
Females				
Metabolic syndrome	HR	Ref.	1.409 (1.028–1.931)	1.956 (1.446–2.646)
	P	—	.033	<.001
Nonfatal cardiovascular disease	HR	Ref.	0.965 (0.534–1.742)	1.262 (0.711–2.238)
	P	—	.905	.427

BP = combined systolic and diastolic blood pressure subgroups, DBP = diastolic blood pressure, HR = hazard ratio, SBP = systolic blood pressure. Hazard ratio was adjusted for age, body mass index, and life style including work, sports, alcohol consumption, and smoking.

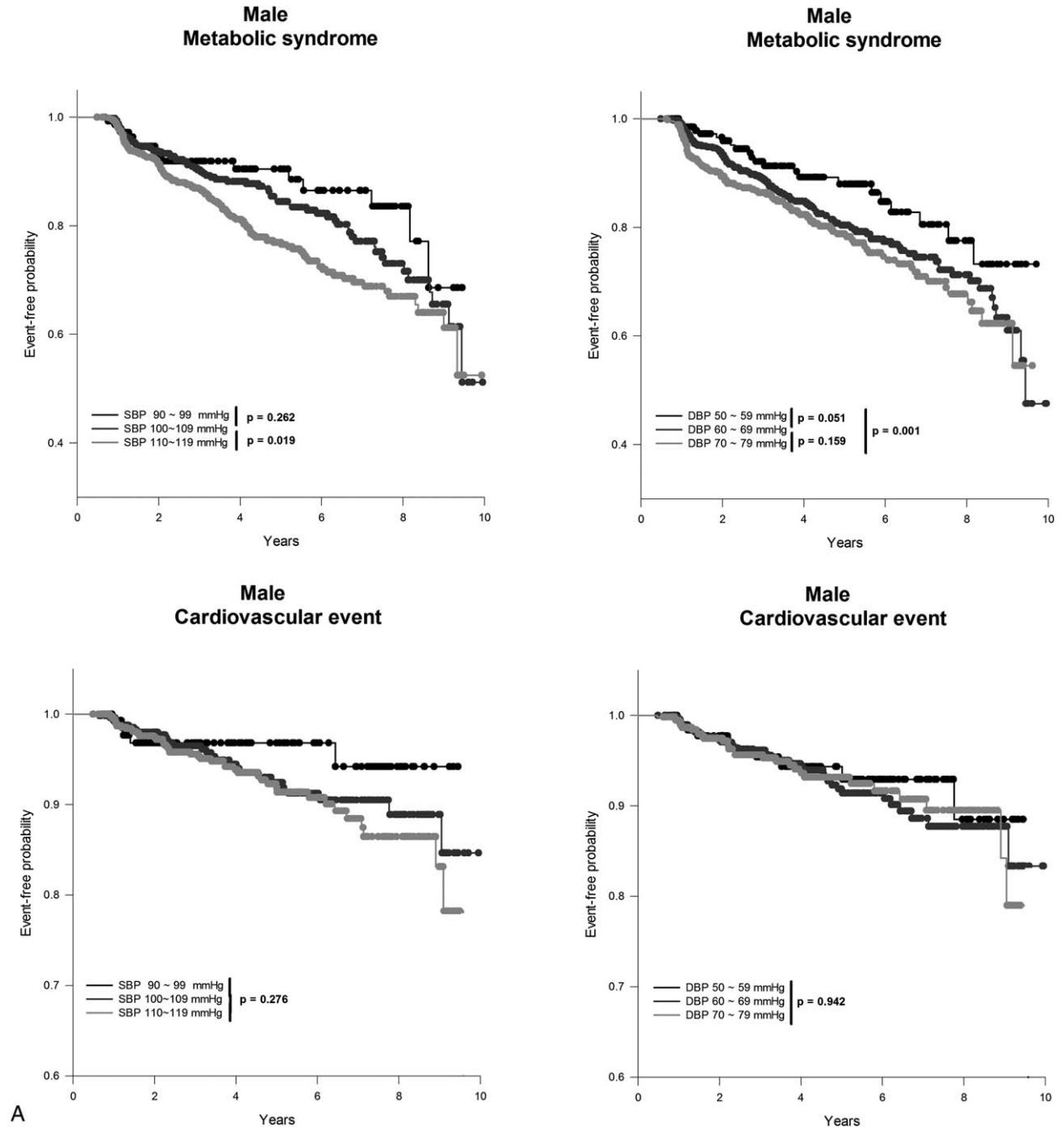

Figure 1. Kaplan-Meier estimates of metabolic syndrome and nonfatal cardiovascular disease for different normal systolic and diastolic blood pressure levels. (A) Males. (B) Females. DBP = diastolic blood pressure, SBP = systolic blood pressure.

be the reason why the association between DBP and FPG was diminished.

Dyslipidemia, either elevation of LDL-C and TG or a decrease in HDL-C, also plays a major role in the development of MetS, CVD, and diabetes. Most of the available data indicate that the HDL-C level is either lower or no different in subjects with prehypertension, compared to those with normotension.[4,6,7,24,26,30–32] In contrast to HDL-C, a higher level of LDL-C starts to emerge in subjects with prehypertension, as was demonstrated in many studies.[4,6,24,26,31] In the present study, we discovered that HDL-C was associated with SBP3 and DBP3 in both sexes, but only with SBP2 and DBP2 in females, during the follow-up period. This finding indicated that HDL-C might have more impact on females than males.

The results of the present study were consistent with our previous studies. Our previous cross-sectional studies showed that normotensive adult and elderly participants with the highest SBP tertile had higher chances of having MetS than those with the lowest tertile. In the present study, subjects with higher normotensive BP still have higher chances of having MetS at baseline. Moreover, we added information regarding the same findings for DBP and combined SBP/DBP analysis. The SBP and DBP ranges were determined for easier clinical application from the study results. In summary, high normotensive BP still

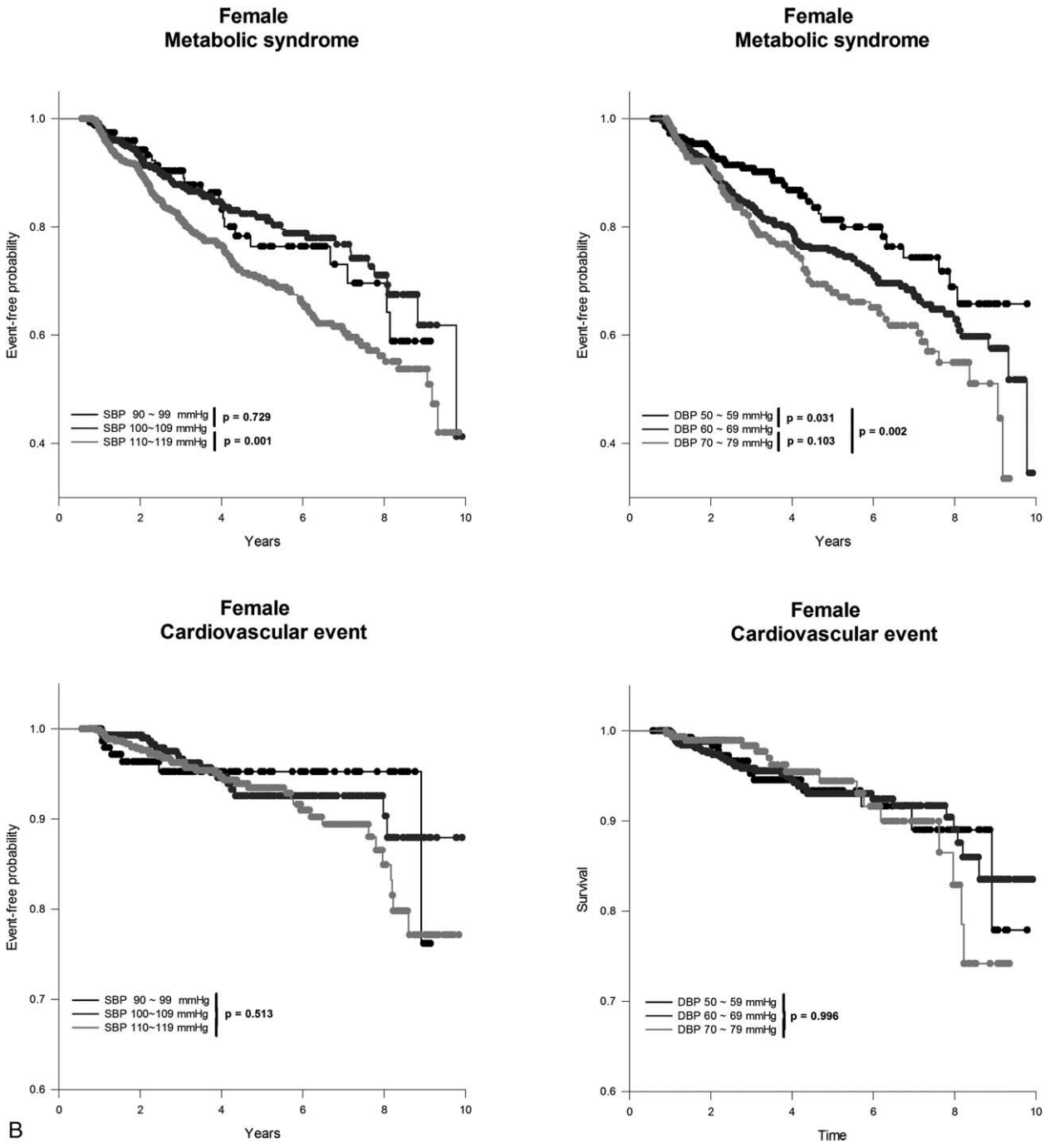

Figure 1B. *(Continued)*

indicates a higher risk of having future MetS, but not CVD. Control of BP to <110/70 mmHg in males and 100/60 mmHg in females seems to be protective against the development of future MetS. However, the risk of developing future nonfatal CVD among 3 groups of either normotensive SBP or DBP was not observed. This may imply that the goal of BP control in the normotensive range is appropriate. Nonetheless, the study design used was collecting questionnaires data from 2 academic hospitals and 1 health screening center, which will create some bias. If fatal CVD develops or serious sequelae deriving from CVD present, these subjects will be less likely to be observed during follow-up. On the contrary, this is the first study demonstrating that normotensive subjects do not have an increased risk of future nonfatal CVD. However, more studies are still needed and further investigation is required to validate the present results.

The major strength of the present study is that it was a longitudinal study to further explore the role of BP in the development of future MetS or CVD in the elderly. In addition, we examined the effect of sex on the risk of MetS components and its development. Furthermore, we used stringent exclusion criteria, reducing the confounding effects of medications to make our results more robust. This kind of design has not been used in most similar studies, which have included subjects who

were taking medications that are known to affect blood glucose, lipids, or BP.

However, our study still had some limitations. First, the follow-up period of this study was up to 10 years. A longer follow-up might have enhanced the clinical value of this observational study, by demonstrating the harmful end-organ effects of BP more clearly, as well as the progression to CVD. In addition, not all of the study participants had regular annual health checkups. Second, we did not have available data on all-cause mortality, which might have influenced the interpretation of the results. Third, part of the questionnaires data was obtained from one health screening center, which may affect the results of the study. If a fatal CVD or major sequelae was to develop, these subjects will have had a higher chance of being lost to follow-up. Finally, the present study only included normotensive study participants. The findings will have limited generalizability owing to a focus on a particular region.

5. Conclusions

High normotensive elderly individuals have a higher risk of developing MetS at baseline and within 10 years of follow-up, but they are not at increased risk of CVD. Based on these findings, we believe that preventive interventions, such as lifestyle modification, should be offered early even to the apparently healthy elderly.

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References

[1] Kannel WB, Gordon T, Schwartz MJ. Systolic versus diastolic blood pressure and risk of coronary heart disease. The Framingham study. Am J Cardiol 1971;27:335–46.
[2] Foldes E. Diabetes and hypertension. Am J Med 1947;3:145–54.
[3] Grorud AC. Hypertension and diabetes. South Dakota J Med 1948; 1:48–51.
[4] Cordero A, Laclaustra M, Leon M, et al. Prehypertension is associated with insulin resistance state and not with an initial renal function impairment. A Metabolic Syndrome in Active Subjects in Spain (MESYAS) Registry substudy. Am J Hypertens 2006;19:189–96. discussion 197–8.
[5] Ferguson TS, Younger NO, Tulloch-Reid MK, et al. Prevalence of prehypertension and its relationship to risk factors for cardiovascular disease in Jamaica: analysis from a cross-sectional survey. BMC Cardiovasc Disord 2008;8:20.
[6] Grotto I, Grossman E, Huerta M, et al. Prevalence of prehypertension and associated cardiovascular risk profiles among young Israeli adults. Hypertension 2006;48:254–9.
[7] Kawamoto R, Kohara K, Tabara Y, et al. Insulin resistance and prevalence of prehypertension and hypertension among community-dwelling persons. J Atheroscler Thromb 2010;17:148–55.
[8] Onat A, Yazici M, Can G, et al. Predictive value of prehypertension for metabolic syndrome, diabetes, and coronary heart disease among Turks. Am J Hypertens 2008;21:890–5.
[9] Player MS, Mainous AG3rd, Diaz VA, et al. Prehypertension and insulin resistance in a nationally representative adult population. J Clin Hypertens 2007;9:424–9.
[10] Yu D, Huang J, Hu D, et al. Association between prehypertension and clustering of cardiovascular disease risk factors among Chinese adults. J Cardiovasc Pharmacol 2009;53:388–400.
[11] Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. J Am Med Assoc 2003;289:2560–72.
[12] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetic Med 1998;15:539–53.
[13] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). J Am Med Assoc 2001;285:2486–97.
[14] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. J Am Med Assoc 2002;287:356–9.
[15] Hwang LC, Bai CH, Chen CJ. Prevalence of obesity and metabolic syndrome in Taiwan. J Formos Med Assoc 2006;105:626–35.
[16] Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–67.
[17] Pei D, Chen YL, Tang SH, et al. Relationship of blood pressure and cardiovascular disease risk factors in normotensive middle-aged men. Medicine 2011;90:344–9.
[18] Er LK, Chen YL, Pei D, et al. Increased incidence of metabolic syndrome in older men with high normotension. Aging Male 2012;15:227–32.
[19] Hsu CH, Lin JD, Wu CZ, et al. High normotension is associated with higher metabolic syndrome risk in postmenopausal women. Geriatr Gerontol Int 2014;14:293–300.
[20] Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation 2005;111:697–716.
[21] Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120: 1640–5.
[22] World Health Organization. Cardiovascular diseases (CVDs). Available at: http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed April 30, 2017.
[23] Okosun IS, Boltri JM, Anochie LK, et al. Racial/ethnic differences in prehypertension in American adults: population and relative attributable risks of abdominal obesity. J Hum Hypertens 2004;18:849–55.
[24] Yu D, Huang J, Hu D, et al. Prevalence and risk factors of prehypertension among Chinese adults. J Cardiovasc Pharmacol 2008;52:363–8.
[25] Kulie T, Slattengren A, Redmer J, et al. Obesity and women's health: an evidence-based review. J Am Board Fam Med 2011;24:75–85.
[26] Tsai PS, Ke TL, Huang CJ, et al. Prevalence and determinants of prehypertension status in the Taiwanese general population. J Hypertens 2005;23:1355–60.
[27] Sowers JR. Insulin resistance and hypertension. Am J Physiol Heart Circ Physiol 2004;286:H1597–602.
[28] Edelson GW, Sowers JR. Insulin resistance in hypertension: a focused review. Am J Med Sci 1993;306:345–7.
[29] Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2011;123:2434–506.
[30] Oda E, Kawai R. High-density lipoprotein cholesterol is positively associated with hypertension in apparently healthy Japanese men and women. Br J Biomed Sci 2011;68:29–33.
[31] Oda E, Kawai R. LDL cholesterol is associated with blood pressure in Japanese women. Diabetes Care 2009;32:e113.
[32] LeRoith D. Dyslipidemia and glucose dysregulation in overweight and obese patients. Clin Cornerstone 2007;8:38–52.