Medicine®

OPEN

High-normal blood pressure conferred higher risk of cardiovascular disease in a random population sample of 50-year-old men
A 21-year follow-up

Xiaojing Chen, MD, PhD, FESC[a,b,*], Salim Bary Barywani, MD, PhD[b], Per-Olof Hansson, MD, PhD[b], Annika Rosengren, MD, PhD[b], Erik Thunström, MD, PhD[b], You Zhong, MD, PhD[b,c], Constantinos Ergatoudes, MD[b], Zacharias Mandalenakis, MD, PhD[b], Kenneth Caidahl, MD, PhD[b,d], Michael Fu, MD, PhD, FESC[b]

Abstract

The relationship between various categories of blood pressure (BP), subtypes of hypertension, and development of cardiovascular disease (CVD) have not been extensively studied. Therefore, our study aimed to explore this relationship in a random population sample of men born in 1943, living in Sweden and followed over a 21-year period.

Participants were examined for the first time in 1993 (age 50 years), where data on medical history, concomitant diseases, and general health were collected. The examination was repeated in 2003 and with additional echocardiography also in 2014. Classification of participants according to their BP at the age of 50 years was as follows: optimal-normal BP (systolic blood pressure [SBP] <130 and diastolic BP [DBP] <85 mmHg), high-normal BP (130 ≤ SBP < 140, 85 ≤ DBP < 90 mmHg), isolated systolic-diastolic hypertension (ISH-IDH) (SBP ≥140 and DBP <90 or SBP <140 and DBP ≥90 mmHg), and systolic-diastolic hypertension (SDH) (SBP ≥140 and DBP ≥90 mmHg).

During the follow-up, the incidence of heart failure (HF), CVD, and coronary heart disease were all lowest for those with optimal-normal BP. Participants with high-normal BP showed greater wall thickness and left ventricular mass index, larger LV size and larger left atrial size when compared with the optimal-normal BP group. Furthermore, those with high-normal BP, ISH-IDH, and SDH had a higher risk of CVD than those with optimal-normal BP. The adjusted relative risk of CVD was highest for SDH (hazard ratio [HR] 1.95; 95% confidence interval [95% CI] 1.37–2.79), followed by ISH-IDH (HR 1.34; 95% CI 0.93–1.95) and high-normal BP (HR 1.31; 95% CI 0.91–1.89).

Over a 21-year follow-up, the participants with high-normal BP or ISH-IDH had a higher relative risk of CVD than those with optimal-normal BP.

Abbreviations: 95% CI = confidence interval, BMI = body mass index, BP = blood pressure, CHD = coronary heart disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, DT = deceleration time, ECGs = electrocardiograms, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, HF = heart failure, HRs = hazard ratios, ISH = isolated systolic hypertension, IVS = interventricular septal thickness, LAA = left atrial area, LDL = low-density lipoprotein, LVEDD = left ventricular end diastolic

1. Introduction

Observational, population-based studies have demonstrated that higher blood pressure (BP) is associated with increased cardiovascular risk and all-cause mortality.[1–13] Different categories of BP are studied in diverse adult age groups in normal cohort populations.[14–22] Isolated systolic hypertension (ISH), an elevated systolic BP (SBP) with a normal or low diastolic BP (DBP), has been shown to be associated with a higher risk of incident heart failure (HF).[22] Tsimploulis et al[19] demonstrated that younger and middle-aged (mean age 34 years) adults with ISH had a higher relative risk of cardiovascular disease (CVD) mortality over 31 years of follow-up compared with those with optimal BP. However, the long-term outcome of persons with high-normal blood pressure was not adequately addressed. Kondo et al[14] showed that high-normal BP is an independent risk factor for CVD in middle-aged (mean age 30 years) adults but not in the elderly. Both studies used young cohorts and did not represent middle-aged adults. In the Japanese study cardiovascular events increased at normal and high-normal BP in young and middle-aged Japanese male smokers but not in nonsmokers.[15] Therefore, the available data on the impact of high-normal BP in middle-aged individuals on cardiovascular risk are not convincing. The present study sought to investigate the impact of all BP categories in particular high-normal BP on cardiovascular risk, including HF, CVD events, and coronary heart disease (CHD).

2. Methods

2.1. Study population

The study of men born in 1943 is a prospective cohort study consisting of a random sample of half of all men born in 1943 and living in the city of Gothenburg, Sweden. Through the census register of the city, 1463 men were contacted and invited to participate in the investigation, which included questionnaires and physical examination procedures. In 1993, 798 men (now aged 50 years) agreed to take part in the study. Those men who were still a resident of Gothenburg and alive were invited to repeat the examination in 2003 and 2014. Follow-up and comorbidity data were collected by the Swedish Hospital Discharge Registry for all participants from 1993 to 2014. The study follows the Declaration of Helsinki and was approved by the Gothenburg Regional Research Ethic Board. All participants gave informed consent to participate in the study.

2.2. Data collection

At each screening, a clinical examination and laboratory analysis were performed and questionnaire data about lifestyle were collected. In addition, in 2014 all study participants underwent an echocardiography evaluation. Fasting venous blood samples were drawn in the morning. Frozen samples of whole blood, plasma, and serum as well as urine were kept at −80°C until analysis. Plasma levels of cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, fasting glucose, and pro-brain natriuretic peptide (NT-pro-BNP) were analyzed using standard laboratory procedures. Body weight was measured with a balance scale to the nearest 0.1 kg, with the men wearing light clothing; height was measured to the nearest cm without shoes; and body mass index (BMI) was calculated in the standard way as kg/m^2. Standard 12-lead electrocardiograms (ECGs) were recorded at a paper speed of 50 mm/s, the standard speed in Sweden. All ECGs were evaluated by a physician who was blinded to the clinical data.

Before the examination, all participants had completed a postal questionnaire about smoking habits, physical activity, family medical history, mental stress, and previous disease. Smoking habits were coded as never smoked, ex-smoker, smoking 1 to 14 g/d, smoking 15 to 24 g/d, and smoking >25 g/d. Grades 1 and 2 were combined into a single group (nonsmokers) while grades 3, 4, and 5 were combined to form a second group (current smokers). Physical activity during leisure time was introduced at each examination and classified into 4 categories mainly sedentary, moderate exercise during leisure time, regular exercise and training, and hard exercise or competitive sports. Categories 2, 3, and 4 were combined (physically active) and category 1 was defined as a sedentary lifestyle.

In 2014, all study participants underwent a standard echocardiography examination. Standard echocardiographic views were acquired with the patient lying in the left lateral decubitus position using a commercially available ultrasound machine (Vivid 7, GE Healthcare, Milwaukee, WI) by the same observer. The parameters measured in the echocardiographic examination were interventricular septal thickness (IVS), left ventricular end diastolic dimension (LVEDD), left ventricular posterior wall thickness (LVPWT), left ventricular ejection fraction (LVEF), and left atrial area (LAA). Transmitral Doppler flow was obtained from the apical 4-chamber view in which E velocity, deceleration time (DT) of the E wave, A velocity, and E/A ratio were measured. Early diastolic mitral annular velocity (e') was measured at the septal site while the E/e' ratio was calculated to estimate LV filling pressure as well as LV diastolic dysfunction.

2.3. Measurement of blood pressure and classification blood pressure groups

BP was recorded, by a trained physicians in our research group, in the right arm with the participant seated. After a 5-minute interview, all BP measurements were recorded to the nearest 2 mmHg in the sitting position using a mercury sphygmomanometer with a cuff size of 12×32 cm. DBP was recorded as both Korotkoff phase IV and V (however, we used only Korotkoff phase V in this study).

Participants were stratified into 4 hypertensive subtypes based on BP values according to the definition of classification of office blood pressure and definitions of hypertensions grade from the 2018 ESC/ESH guidelines for the management of arterial

hypertension: optimal-normal BP (SBP <130 mmHg and DBP <85 mmHg), high-normal BP (130 mmHg ≤ SBP < 140 mmHg, 85 mmHg ≤ DBP < 90 mmHg), isolated systolic-diastolic hypertension (ISH-IDH): (SBP ≥140 mmHg and DBP <90 mmHg or SBP <140 mmHg and DBP ≥90 mmHg), systolic-diastolic hypertension (SDH) (SBP ≥140 mmHg and DBP ≥90 mmHg).

2.4. Follow-up procedures and endpoints

All participants were followed-up by reexaminations from 1993 to 2014. Outcome and clinical data were collected for all participants by reviewing medical charts through the Swedish Hospital Discharge Registry and the Swedish Death Registry from 1993 to 2014. Endpoint CVD is defined by the occurrence of myocardial infarction, HF, death resulting from CHD (410–414; I20–21), stroke, intermittent claudication, other cardiovascular death, and revascularization procedure. All deaths and suspected CVD were reviewed by a panel of 5 physicians. Total HF events included HF that occurred during follow-up preceding final examination with echocardiography, those who died because of HF and newly detected HF upon final examination in 2014 with echocardiography.

2.5. Statistical analysis

Descriptive statistics are presented as frequencies and percentages for categorical variables and mean ± standard deviation for continuous variables. Differences in the distribution of baseline characteristics in the different BP categories were analyzed using the chi-square trend test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. For blood pressure levels shown in Table 1, and for all variables of Table 2, when the ANOVA showed a P-value <.01, we performed unpaired t test of each other blood pressure group versus the optimal-normal group.

Univariable- and multivariable-adjusted Cox proportional hazard models were used to examine the association of high-normal BP, ISH-IDH and SDH, and outcomes. Using optimal-normal BP as the reference group, unadjusted and multivariate-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated for each hypertension subtype. The multivariable model was adjusted for smoking, sedentary lifestyle, BMI, heart rate, triglyceride, and estimated glomerular filtration rate (eGFR). We also used the same multivariable Cox proportional hazard models to analyze time at risk of CVD, CHD, and the association with different BP cut-off levels.

Table 1

Baseline characteristics (1993) as a function of BP group and hypertension subtype.

	Optimal-normal BP (n = 339)	High-normal BP (n = 156)	ISH-IDH (n = 154)	SDH (n = 146)	P-value
SBP in 1993, mmHg	115.2 ± 8.5	128.5 ± 7.6	135.2 ± 12.1	153.5 ± 11.8	<.001
DBP in 1993, mmHg	75.7 ± 5.9	84.4 ± 4.5	90.0 ± 6.1	98.8 ± 7.2	<.001
SBP in 2003, mmHg	134.4 ± 16.7	146.9 ± 17.5	148.9 ± 17.7	156.8 ± 20.0	<.001
DBP in 2003, mmHg	80.7 ± 8.8	87.4 ± 10.1	87.8 ± 9.7	90.6 ± 11.3	<.001
SBP in 2014, mmHg	141.7 ± 19.2	144.9 ± 17.4	147.0 ± 17.1	149.6 ± 15.1	.013
DBP in 2014, mmHg	80.7 ± 9.4	83.2 ± 11.5	85.8 ± 9.9	84.4 ± 9.4	.001
Clinical characteristics					
Smoking (%)	108 (31.9)	59 (37.8)	43 (27.9)	47 (32.2)	.255
Never smoker					
Former smoker	114 (33.6)	58 (37.2)	62 (40.3)	58 (39.7)	
Current smoker	117 (34.5)	39 (25)	49 (32)	41 (28)	
Sedentary lifestyle	40 (11.8)	21 (13.5)	32 (20.8)	29 (19.9)	.023
Sleeping time per night, h	7.0 ± 1.0	6.9 ± 0.8	6.9 ± 1.0	7.0 ± 0.9	.926
Mental stress	51(15.0)	19 (12.3)	28 (18.5)	25 (17.1)	.449
BMI, kg/m^2	25.3 ± 2.9	25.8 ± 3.1	27.1 ± 3.5	28.1 ± 3.9	<.001
Waist circumference, cm	92.4 ± 8.1	94.2 ± 8.4	97.9 ± 9.6	99.9 ± 10.9	<.001
Heart rate, bpm	64.6 ± 11.2	67.6 ± 13.1	68.3 ± 12.7	71.1 ± 12.3	<.001
Medical history (%)					
Hyperlipidemia	7 (6.5)	13 (5.2)	13 (5.2)	17 (8.9)	.371
Hyperlipidemia	13 (3.9)	6 (3.8)	5 (3.2)	10 (6.0)	.368
Atrial fibrillation	3 (1)	1 (1)	2 (1)	3 (2)	.641
Diabetes	6 (2)	4 (2.5)	3 (1.9)	7 (4.8)	.210
Stroke	1 (0.3)	1 (0.6)	0 (0)	0 (0)	.634
Lung disease	25 (7.4)	12 (7.7)	10 (6.5)	9 (6.2)	.940
Laboratory characteristic					
Cholesterol, mmol/L	5.8 ± 1.1	6.0 ± 1.1	5.9 ± 0.9	6.0 ± 1.0	.084
Triglyceride, mmol/L	1.5 ± 0.9	1.7 ± 1.5	1.6 ± 0.8	2.1 ± 1.4	<.001
HDL, mmol/L	1.4 ± 0.4	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	.195
Plasma glucose, mmol/L	4.5 ± 1.0	4.8 ± 1.7	4.7 ± 1.4	5.2 ± 1.9	<.001
Creatinine, mmol/L	89.8 ± 10.6	91.8 ± 10.3	91.1 ± 9.0	93.1 ± 10.1	.007
eGFR	100.3 ± 20.2	101.4 ± 16.2	105.1 ± 17.5	107.1 ± 19.5	.001
NT pro BNP, pg/mL	32.3 ± 39.0	30.6 ± 31.8	36.8 ± 40.4	46.4 ± 60.1	.005
Hs-cTnT	4.8 ± 2.9	5.2 ± 3.8	5.0 ± 2.5	5.9 ± 4.5	.022

BMI = body mass index, BP = blood pressure, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, Hs-cTnT = higher sensitive cardiac troponin T, NT-pro-BNP = pro-brain natriuretic peptide, SBP = systolic blood pressure.
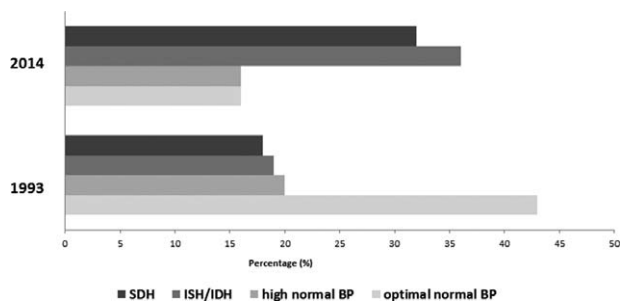
Figure 1. Distribution of blood pressure groups in 1993 and 2014.

All statistical tests were two-tailed with 95% CI and *P*-values of <.05 were considered statistically significant. IBM SPSS Statistics for Windows, Version 22 was used for data analysis.

3. Results

3.1. Prevalence of blood pressure categories and hypertensive subtypes in 1993

Overall, the mean SBPs were 128.7 ± 17.1 mmHg in 1993 and 144.4 ± 18.1 mmHg in 2014; mean DBPs were 84.4 ± 10.6 mmHg in 1993 and 82.6 ± 10.1 mmHg in 2014. Participants with optimal-normal blood pressure were almost 3-fold more in 1993 (43%) compared with 2014 (16%). Inversely, participants with ISH-IDH and SDH were almost 2-fold more frequent in 2014 (ISH-IDH: 36%, SDH: 32%) than in 1993 (ISH-IDH: 19%, SDH: 18%) (Fig. 1).

3.2. Baseline characteristics in 1993

Demographic and clinical characteristics of the participants in 1993 by BP category and hypertension subtype are shown in

Table 1. Participants in the SDH and ISH-IDH groups had a higher BMI and larger waist circumference, as well as higher triglyceride, plasma glucose, creatinine, and NT-pro-BNP levels. These participants were more likely to lead a sedentary lifestyle and present with a higher heart rate than participants in the optimal-normal BP groups.

3.3. The relationship between baseline BP in 1993 and heart function as measured by echocardiography

Echocardiographic evaluation of LV systolic and diastolic function in the BP groups at the 21-year follow-up is illustrated in Table 2. Participants in the SDH, ISH-IDH, and high-normal groups showed greater septal wall thickness than the optimal-normal BP group. Those in the high-normal group had a larger LV EDD and end diastolic volume also when corrected for BSA compared with the optimal-normal group. Both this group and those with SDH had a larger left atrial area and the latter had also indication of higher filling pressure (E/e') when compared with the optimal-normal BP group.

3.4. Relationship between baseline BP in 1993 and outcome

During the 21-year follow-up, the incidence of HF, CVD, and CHD were all lowest for those with optimal-normal BP (Table 3 and Fig. 2). Results from the Cox proportional hazards models, which was adjusted for clinical characteristics (smoking, sedentary lifestyle, BMI, heart rate, triglyceride, and eGFR), suggested that high-normal BP, ISH-IDH, and SDH were associated with a higher risk of CVD and CHD in comparison with optimal-normal BP. The adjusted relative risk of CVD mortality was highest for SDH (HR 1.95; 95% CI 1.37–2.79), followed by ISH-IDH (HR 1.34; 95% CI 0.93–1.95) and high-normal BP (HR 1.31; 95% CI 0.91–1.89). The adjusted HR for

Table 2

Systolic and diastolic heart function as measured by echocardiography in 2014 by BP group (n=536).

	Optimal-normal BP (n=242)	High-normal BP (n=112)	ISH-IDH (n=98)	SDH (n=82)	*P*-value	Criteria
LV structure						
LV septal wall thickness, mm	10.3 ± 1.5	$10.7 \pm 1.6^*$	$10.7 \pm 1.2^*$	$10.6 \pm 1.5^*$	<.001	
EDD, mm	48.5 ± 5.0	$50.4 \pm 6.0^*$	49.6 ± 6.6	48.7 ± 5.9	.021	
EDV, mL	111.9 ± 26.2	$122.9 \pm 37^*$	118.8 ± 36.5	113.4 ± 32.2	.014	
EDV/BSA, mL/m²	56.0 ± 12.5	$60.3 \pm 18.1^*$	57.3 ± 16.3	54.7 ± 15.9	.043	
LV enlargement, %	83 (24)	48 (31)	40 (26)	28 (19)	.137	EDV/BSA >60.2
LV mass index, g/m²	91.3 ± 23.7	$96.3 \pm 25.0^*$	$97.3 \pm 23.2^*$	$96.4 \pm 23.6^*$	.082	
LVH, %	27 (8)	21 (13)	25 (16)	17 (12)	.041	LVMI >115
LV systolic function						
LVEF, %	61.9 ± 7.4	61.4 ± 9.2	$60.0 \pm 8.3^*$	61.4 ± 9.8	.276	
LVEF, 40%–49%	10 (3)	10 (6)	10 (6)	5 (3)	.141	
LVEF, <40%	2 (0.5)	3 (2)	2 (1)	3 (2)	.355	
LV diastolic function						
TDI e'_{septal}	6.6 ± 1.6	6.5 ± 1.7	$6.2 \pm 2.1^*$	6.3 ± 2.1	.104	
Abnormal e'	19 (6)	16 (10)	19 (12)	13 (9)	.064	TDI e'_{septal} <4.3
E/e'	9.3 ± 3.0	9.9 ± 3.4	9.7 ± 3.0	$10.8 \pm 4.6^*$	.010	
Abnormal E/e'	12 (3)	7 (4)	8 (5)	7 (4)	.830	E/e' >14.8
LAA, cm²	21.7 ± 4.5	$23.1 \pm 5.6^*$	22.3 ± 4.9	$23.8 \pm 5.1^*$	.005	
LAVI, mL/m²	33.2 ± 10.2	$35.8 \pm 11.4^*$	32.4 ± 11.3	35.0 ± 11.6	.069	
Abnormal LAVI	92 (27)	56 (36)	34 (22)	34 (23)	.028	>34.2

BP = blood pressure, BS = body surface area, EDV = end diastolic volume, ISH-IDH = isolated systolic-diastolic hypertension, LAA = left atrial area, LAVI = left atrial volume index, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy, SDH = systolic-diastolic hypertension, TDI = tissue doppler imaging, EDD = end diastolic dimension.

* *P* < .05 when compared with the optimal-normal BP group.

Table 3

Outcome by BP group.

	Number at risk	Number at different stages	Unadjusted		Adjusted	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Heart failure						
Optimal-normal BP	339	29 (9)	Reference group		Reference group	
High-normal BP	156	22 (14)	1.68 (0.96–2.92)	.067	1.63 (0.93–2.85)	.090
ISH-IDH	154	15 (10)	1.14 (0.61–2.12)	.688	0.89 (0.47–1.68)	.709
SDH	146	26 (18)	2.19 (1.29–3.72)	.004	1.51 (0.84–2.70)	.170
Cardiovascular disease						
Optimal-normal BP	339	78 (23)	Reference group		Reference group	
High-normal BP	156	46 (29)	1.34 (0.93–1.93)	.117	1.31 (0.91–1.89)	.153
ISH-IDH	154	49 (32)	1.51 (1.05–2.15)	.025	1.34 (0.93–1.95)	.118
SDH	146	63 (43)	2.23 (1.60–3.11)	<.001	1.95 (1.37–2.79)	<.001
Coronary heart disease						
Optimal-normal BP	339	34 (10)	Reference group		Reference group	
High-normal BP	156	21 (13)	1.33 (0.77–2.29)	.309	1.21 (0.70–2.11)	.491
ISH-IDH	154	23 (15)	1.58 (0.93–2.68)	.090	1.42 (0.83–2.45)	.204
SDH	146	35 (24)	2.58 (1.61–4.13)	<.001	2.10 (1.26–3.49)	.005
All-cause death						
Optimal-normal BP	339	46 (14)	Reference group		Reference group	
High-normal BP	156	16 (10)	0.73 (0.42–1.29)	.284	0.66 (0.37–1.18)	.158
ISH-IDH	154	31 (20)	1.55 (0.99–2.45)	.058	1.40 (0.87–2.25)	.162
SDH	146	26 (18)	1.34 (0.83–2.17)	.24	1.14 (0.68–1.91)	.627

Multivariate model adjusted for smoking, sedentary lifestyle, BMI, heart rate, triglyceride, and eGFR.
BP = blood pressure, CI = confidence interval, ISH-IDH = isolated systolic-diastolic hypertension, OR = odds ratio, SDH = systolic-diastolic hypertension.

CHD was also highest for SDH (HR 2.10; 95% CI 1.26–3.49), followed by ISH-IDH (HR 1.42; 95% CI 0.83–2.45) and high-normal BP (HR 1.21; 95% CI 0.70–2.11). However, although the incidence of HF was highest in the SDH group and lowest in the optimal-normal BP group, in the unadjusted model SDH was associated with a higher risk of HF compared with optimal-normal BP (HR 2.19; 95% CI 1.29–3.72). When adjusted for the other clinical characteristics, no significant association was found with HF.
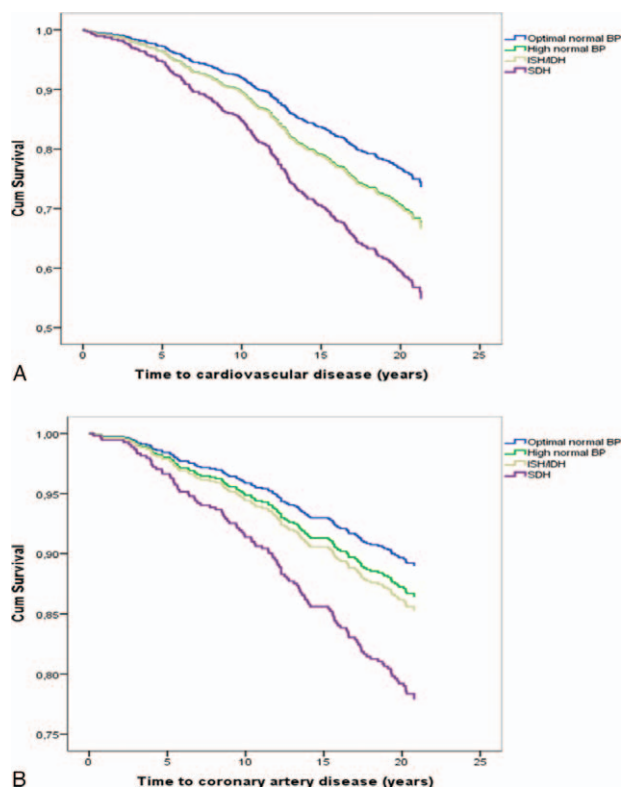
Figure 2. Adjusted risk for outcome of cardiovascular disease and coronary artery disease by different blood pressure groups.
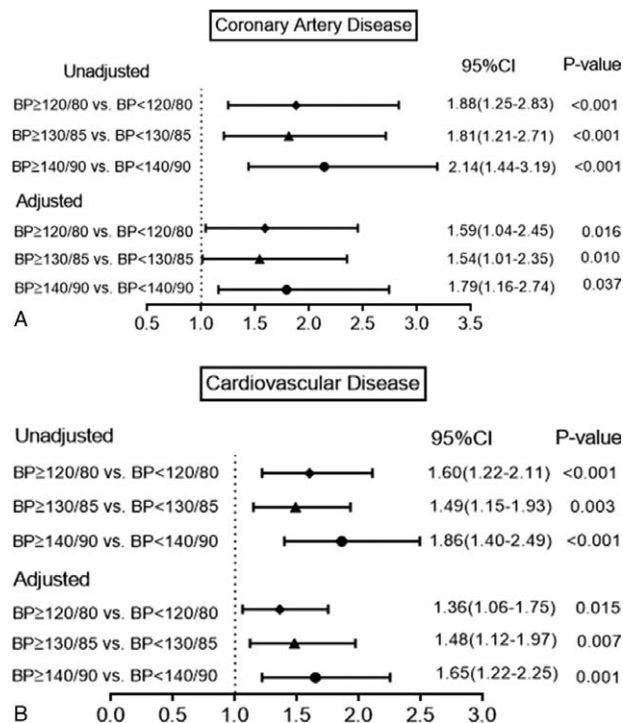
Figure 3. The forest plot illustrates the univariate and multivariate logistic regression model used to assess the relationship between different cut-off values for systolic and diastolic blood pressure associated with cardiovascular and coronary artery disease. A multivariate model was adjusted for smoking, sedentary lifestyle, body mass index, heart rate, triglyceride, and glomerular filtration rate.

Figure 3 depicts multivariable adjusted HRs for CVD and CHD as a function of BP cut-off values. The highest risk was in the highest SBP/DBP category where multivariable adjusted HR for incident CVD was 1.65 (95% CI 1.22–2.25) and for CHD 1.79 (95% CI 1.16–2.74), with BP ≥140/90 mmHg compared with BP <140/90 mmHg. The HRs were also significantly higher in the 2 lower SBP categories. In addition, we found that even participants with BP ≥120/80 mmHg in 1993 had a 1.36-fold increased risk of CVD and a 1.59-fold increased risk of CHD compared with those with BP <120/80 mmHg.

4. Discussion

The main finding here is that combined SDH in comparison to individuals with optimal normal BP is associated with the highest risk of CVD events, followed by ISH-IDH and high-normal BP. CVD events are defined as a composite of CHD (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and HF. Furthermore, the analyses, performed using different BP cut-off values, demonstrate that the risk of CVD events increases with increasing BP (Fig. 3).

CHD and HF as important cardiovascular events are used as secondary endpoints. The adjusted HR for CHD was also highest for SDH, followed by ISH-IDH and high-normal BP. SDH was found to increase with age and it was the most common hypertensive subgroup in the age group 70 years, suggesting that BP <120/80 mmHg was the safest BP level at the age of 50 years for CVD events and CHD. Our results indicate that BP increases with age, resulting in increased organ damage, regardless of the BP components (systolic or diastolic). However, SDH proved to be the worst hypertensive subgroup. Smoking, sedentary lifestyle, high BMI, triglycerides, eGFR, NT-proBNP, wider waist circumference and higher heart rate occurred more often in the ISH-IDH and SDH groups. We adjusted for these risk factors in our analyses (Table 3).

The association between higher BP than optimal-normal BP and an increased risk of CVD events is supported by the biomarkers and cardiac changes detected by echocardiography in the participants aged 70 years. Compared with those in the optimal-normal BP group, participants in other BP categories, especially SDH, had a thicker septal wall, higher LVMI, higher E/e~, larger left atrium, higher levels of NT-ProBNP, and higher sensitive cardiac troponin T (Hs-cTnT) (Tables 1 and 2).

Of note, Hs-cTnT was significantly elevated in individuals with SDH, indicating an association between SDH and cardiac myocyte apoptosis.

Patients in the SDH group had a higher mean SDBP (153.5 mmHg) at baseline than in 2014 (149.6 mmHg), to some extent probably because they received HT treatment, albeit suboptimal, which would account for their worse long-term outcomes.

Although the association between increased incidence of HF and elevated BP was not significant, the high levels of NT-proBNP might suggest that some patients in the SDH group had undiagnosed HF.

Comparing with the available data our data is more representative for middle-aged individuals partly because our cohort is a random general population, and partly because the previous studies included young individuals with a mean age around 35 years.[14,15,19] Moreover, our data includes more details on organ damage supporting the results; echocardiogra-phy findings and biomarkers (NT-proBNP) measured in 2014, compared with the available data. Nevertheless, our results are in line with the majority of observations obtained in the field. There is a lot of population based data demonstrating that higher blood pressure is associated with increased cardiovascular risk and all-cause mortality.[1–13,20,23,24] For instance, among older adults, both SDH and ISH have similar independent associations with incident HF, cardiovascular mortality, and other incident cardiovascular events.[20] Some studies have shown that the prevalence of hypertension and metabolic syndrome increases with advanced age.[23] However, our results have added values by showing that high-normal BP is carrying higher risk of CVD events and SDH was more common than ISH in persons aged ≥50 years.[24]

5. Conclusion

For the 50-year-old men living in Gothenburg, SDH is associated with the highest risk of CVD and CHD followed by ISH/IDH and high-normal BP after a 21-year follow-up. BP rises with age, resulting in increased organ damage and adverse cardiovascular effects.

Author contributions

Conceptualization: Xiaojing Chen, Per-Olof Hasson, Michael Fu.
Data curation: Salim Bary Barywani, Per-Olof Hasson, Annika Rosengren, Erik Thunström, You Zhong, Constantinos Ergatoudes, Zacharias Mandalenakis, Kenneth Caidahl, Michael Fu.
Formal analysis: Xiaojing Chen, Salim Bary Barywani.
Funding acquisition: Michael Fu.
Supervision: Michael Fu.
Validation: Xiaojing Chen, Per-olof Hasson, Michael Fu.
Writing – original draft: Xiaojing Chen.
Writing – review & editing: Salim Bary Barywani, Per-Olof Hasson, Annika Rosengren, Erik Thunström, You Zhong, Constantinos Ergatoudes, Zacharias Mandalenakis, Kenneth Caidahl, Michael Fu.

References

[1] Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet* 2014;383:1899–911.

[2] Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. Lancet 2003;362:1527–35.

[3] Kokubo Y, Kamide K, Okamura T, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. Hypertension 2008;52:652–9.

[4] Huang J, Wildman RP, Gu D, et al. Prevalence of isolated systolic and isolated diastolic hypertension subtypes in China. Am J Hypertens 2004;17:955–62.

[5] MacMahon S, Peto R, Cutler J. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765–74.

[6] Vishram JK, Dahlöf B, Devereux RB, et al. Blood pressure variability predicts cardiovascular events independently of traditional cardiovascular risk factors and target organ damage: a LIFE substudy. J Hypertens 2015;33:2422–30.

[7] Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001;358:1305–15.

[8] Wright JTJr, Williamson JD, Whelton PK, et al. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–16.

[9] Stahl CH, Novak M, Lappas G, et al. High-normal blood pressure and long-term risk of type 2 diabetes: 35-year prospective population based cohort study of men. BMC Cardiovasc Disord 2012;12:1–8.

[10] Franklin SS, Barboza MG, Pio JR, Wong ND. Blood pressure categories, hypertensive subtypes, and the metabolic syndrome. J Hypertens 2006;24:2009–16.

[11] Kokubo Y, Kamide K. High-normal blood pressure and the risk of cardiovascular disease. Circ J 2009;73:1381–5.

[12] Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–13.

[13] Hadaegh F, Mohebi R, Khalili D, et al. High normal blood pressure is an independent risk factor for cardiovascular disease among middle-aged but not in elderly populations: 9-year results of a population-based study. J Hum Hypertens 2013;27:18–23.

[14] Kondo T, Osugi S, Shimokata K, et al. Cardiovascular events increased at normal and high-normal blood pressure in young and middle-aged Japanese male smokers but not in nonsmokers. J Hypertens 2013;3:263–70.

[15] Ogliari G, Westendorp RG, Muller M, et al. Blood pressure and 10-year mortality risk in the Milan Geriatrics 75+ Cohort Study: role of functional and cognitive status. Age Ageing 2015;44:932–7.

[16] Kim NH, Cho HJ, Kim YJ, et al. Combined effect of high-normal blood pressure and low HDL cholesterol on mortality in an elderly Korean population: the South-West Seoul (SWS) study. Am J Hypertens 2011;24:918–23.

[17] Sheriff HM, Tsimploulis A, Valentova M, et al. Isolated diastolic hypertension and incident heart failure in community-dwelling older adults: insights from the Cardiovascular Health Study. Int J Cardiol 2017;238:140–3.

[18] Yano Y, Stamler J, Garside DB, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. J Am Coll Cardiol 2015;65:327–35.

[19] Tsimploulis A, Sheriff HM, Lam PH, et al. Corrigendum to "Systolic-diastolic hypertension versus isolated systolic hypertension and incident heart failure in older adults: insights from the cardiovascular health study". Int J Cardiol 2017;238:11–16.

[20] Ekundayo OJ, Allman RM, Sanders PW, et al. Isolated systolic hypertension and incident heart failure in older adults: a propensity-matched study. Hypertension 2009;53:458–65.

[21] Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887–98.

[22] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among U.S. adults: findings from the third National health and Nutrition Examination Survey. JAMA 2002;287:356–9.

[23] Brody DJ, Pirkle JL, Kramer RA, et al. Paschal. Blood lead levels in the US population Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991). JAMA 1988;1994:233–71.

[24] Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An update from the American Society of Echocardiography and the European Association of, Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:412.