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Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life

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IMPORTANCE Little is known regarding the association between level of blood pressure (BP) in young adulthood and cardiovascular disease (CVD) events by middle age.

OBJECTIVE To assess whether young adults who developed hypertension, defined by the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) BP guideline, before age 40 years have higher risk for CVD events compared with those who maintained normal BP.

DESIGN, SETTING, AND PARTICIPANTS Analyses were conducted in the prospective cohort Coronary Artery Risk Development in Young Adults (CARDIA) study, started in March 1985. CARDIA enrolled 5115 African American and white participants aged 18 to 30 years from 4 US field centers (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California). Outcomes were available through August 2015.

EXPOSURES Using the highest BP measured from the first examination to the examination closest to, but not after, age 40 years, each participant was categorized as having normal BP (untreated systolic BP [SBP] <120 mm Hg and diastolic BP [DBP] <80 mm Hg; n = 2574); elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg; n = 445); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg; n = 1194); or stage 2 hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medication; n = 638).

MAIN OUTCOMES AND MEASURES CVD events: fatal and nonfatal coronary heart disease (CHD), heart failure, stroke, transient ischemic attack, or intervention for peripheral artery disease (PAD).

RESULTS The final cohort included 4851 adults (mean age when follow-up for outcomes began, 35.7 years [SD, 3.6]; 2657 women [55%]; 2441 African American [50%]; 206 taking antihypertensive medication [4%]). Over a median follow-up of 18.8 years, 228 incident CVD events occurred (CHD, 109; stroke, 63; heart failure, 48; PAD, 8). CVD incidence rates for normal BP, elevated BP, stage 1 hypertension, and stage 2 hypertension were 1.37 (95% CI, 1.07-1.75), 2.74 (95% CI, 1.78-4.20), 3.15 (95% CI, 2.47-4.02), and 8.04 (95% CI, 6.45-10.03) per 1000 person-years, respectively. After multivariable adjustment, hazard ratios for CVD events for elevated BP, stage 1 hypertension, and stage 2 hypertension vs normal BP were 1.67 (95% CI, 1.01-2.77), 1.75 (95% CI, 1.22-2.53), and 3.49 (95% CI, 2.42-5.05), respectively.

CONCLUSIONS AND RELEVANCE Among young adults, those with elevated blood pressure, stage 1 hypertension, and stage 2 hypertension before age 40 years, as defined by the blood pressure classification in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, had significantly higher risk for subsequent cardiovascular disease events compared with those with normal blood pressure before age 40 years. The ACC/AHA blood pressure classification system may help identify young adults at higher risk for cardiovascular disease events.

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The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) blood pressure (BP) guideline defined elevated BP as clinic-measured systolic BP (SBP) of 120 mm Hg to 129 mm Hg and diastolic BP (DBP) less than 80 mm Hg, and stage 1 hypertension as SBP of 130 mm Hg to 139 mm Hg or DBP of 80 mm Hg to 89 mm Hg.[1] These new definitions lowered the BP thresholds for hypertension from SBP/DBP of 140/90 mm Hg or more[2] to SBP/DBP of 130/80 mm Hg or more,[1] and increased the prevalence of hypertension 2-fold to 3-fold among young adults.[1] Nonpharmacological and pharmacological interventions were recommended for adults with stage 1 hypertension who also have an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher. However, most young adults with stage 1 hypertension have low 10-year ASCVD risk and would not be recommended pharmacological interventions.[3] Furthermore, using the Pooled Cohort Equations risk calculator to estimate 10-year ASCVD risk among adults younger than 40 years is not recommended because the equations were developed and validated among adults aged 40 to 79 years.[4] If stage 1 hypertension is not associated with CVD events in young adults, it suggests the possible overdiagnosis of hypertension in this population that could result in unnecessary treatment.

Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study,[5] we assessed (1) whether adults who developed elevated BP or hypertension before age 40 years have higher risk for CVD events later in life compared with those who maintained normal BP (SBP <120 mm Hg and DBP <80 mm Hg) through age 40 years; and (2) whether the association differs by race and sex.

Key Points

Question Do adults who develop hypertension, defined using the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) blood pressure guideline, before age 40 years have a higher risk for cardiovascular disease events compared with those who maintain normal blood pressure?

Findings In this prospective cohort study of 4851 young adults (aged 18-30 years), elevated blood pressure, stage 1 hypertension, and stage 2 hypertension occurring before age 40 years were each associated with a significantly higher risk for cardiovascular disease events compared with the reference group with normal blood pressure (hazard ratios: 1.67, 1.75, and 3.49, respectively).

Meaning The blood pressure classification in the 2017 ACC/AHA blood pressure guideline may help identify young adults at higher risk for cardiovascular disease events.

Methods

All participants provided written informed consent at each study visit, and institutional review boards at each field center and the coordinating center approved the study annually. The CARDIA study enrolled 5115 African American and white participants aged 18 to 30 years from 4 US field centers (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California) in 1985 and 1986.[5,6] The current study excluded participants who experienced CVD events before age 40 years, participants lost to follow-up before age 40 years, and participants who were missing BP data and covariates needed for the analysis. After the baseline examination (year 0 [Y_0]), follow-up examinations were conducted at years 2 (Y_2), 5 (Y_5), 7 (Y_7), 10 (Y_{10}), 15 (Y_{15}), 20 (Y_{20}), 25 (Y_{25}), and 30 (Y_{30}). Semi-annual contact has been maintained with participants for follow-up of events; 87% of the cohort members have participated in a clinic examination or semi-annual interview over the last 2 years; 92% over the last 5 years.

BP and Other Measurements

During the Y_0 to Y_{15} examinations, trained research staff measured BP 3 times in participants' right-arm brachial artery at 1-minute intervals after the participant had been sitting in a quiet room for 5 minutes, using a random-zero sphygmomanometer (Hawksley). The mean of the second and third measurements were used for the analysis. The standardized BP measurement techniques using validated equipment in this study met the recommendations in the 2017 ACC/AHA BP guideline to obtain accurate BP measurements in the clinic and are described in the eMethods in the Supplement. An automated oscillometric BP monitor (HEM-907XL; Omron) has been used since the Y_{20} examination. A calibration study was performed, and values standardized to the sphygmomanometric measures were used for the Y_{20}, Y_{25}, and Y_{30} BP measurements (eMethods in the Supplement).[7,8] The calibration study's alignment of BP values between the 2 measurement devices should minimize potential misclassification of BP levels.

CARDIA was specifically designed to study African American and white race/ethnicity differences in the development of cardiovascular risk from young adulthood onwards. Race was determined from responses to closed-ended questions about the race of each participant's natural mother and father. Other data (including education level, height, weight, smoking status, physical activity,[9] medication use, history of diabetes and CVD, and fasting laboratory values) were collected using standardized protocols and quality control procedures across study centers at each visit, as described previously.[5,6]

BP Classification and Adjustment for Covariates

The analysis included participants who had BP measurements obtained during 2 or more study examinations before age 40 years. Participants were categorized as having normal BP, elevated BP, stage 1 hypertension, or stage 2 hypertension using all readings from the Y_0 examination to the examination closest to, but not after, age 40 years for each participant. The normal BP group included participants with SBP less than 120 mm Hg and DBP less than 80 mm Hg at every examination attended. The elevated BP group included participants with SBP of 120 mm Hg to 129 mm Hg and DBP less than 80 mm Hg at 1 or more examinations,

and with SBP/DBP less than 130/80 mm Hg at all examinations. The stage 1 hypertension group included participants with SBP of 130 mm Hg to 139 mm Hg or DBP of 80 to 89 mm Hg at 1 or more examinations and with SBP less than 140 mm Hg and DBP less than 90 mm Hg at all examinations. The stage 2 hypertension group included participants with SBP of 140 mm Hg or more, DBP of 90 mm Hg or more, or taking antihypertensive medication at 1 or more examinations. Specific examples for this approach are shown in eFigure 1 in the Supplement.

Cardiovascular Outcomes

Research staff collected information on hospitalizations and outpatient medical procedures during examinations and annual contacts (standardized questionnaires were completed via mail, phone, or email contact). If there were any hospitalizations or outpatient visits, medical records were requested and were used to adjudicate clinical CVD events. Additional semi-annual contacts were conducted (also via mail, phone, or email) and were designed to provide research staff with the opportunity to update participants' contact information. The semi-annual contact also provided an opportunity to assess vital status (the questionnaire on hospitalizations and outpatient medical procedures was not used at this contact). Vital status was also ascertained through periodic searches of the National Death Index. The primary outcome was composite CVD events (fatal and nonfatal coronary heart disease [CHD], hospitalization for heart failure, stroke, transient ischemic attack, or intervention for peripheral artery disease). Definitions of each outcome have been previously described.[10-12] In the primary analysis, if a participant had more than 1 event occur, the first event was counted as the outcome. In end point-specific analyses (sensitivity analysis), if a participant had more than 1 different type of events, each event was counted as an outcome. For example, if a participant had a diagnosis of CHD and then had a stroke a month later, the CHD and stroke events were counted separately as outcomes in end point-specific analyses. All-cause mortality was examined as a secondary outcome; for this analysis, if a participant had CVD events and then died, her/his death was counted as an outcome. Two physician members of the End Points Committee independently reviewed medical records to adjudicate each possible CVD event or underlying cause of death using specific definitions and a detailed manual of operations (eMethods in the Supplement).[6] For the current analysis, outcomes were available through August 2015.

Statistical Analyses

We calculated characteristics for participants in each of the 4 BP groups (ie, normal BP; elevated BP; stage 1 hypertension; and stage 2 hypertension). We calculated the incidence rate of CVD events and all-cause mortality for participants in each BP group. The cumulative incidence of CVD events and all-cause mortality for the 4 BP groups were calculated using the Kaplan-Meier method. Using Cox proportional hazards models, we estimated the hazard ratios (HRs) and 95% CIs for CVD events associated with the 4 BP groups, separately, with the normal BP group as the referent group. As a post hoc analysis, we fit models for subtypes of CVD events (ie, CHD, stroke, and heart failure), separately. The examination date closest to, but not after, age 40 years for each participant was defined as the time origin for time-to-event analysis. Follow-up time was censored on the date of an event ascertainment. Participants who did not have events were censored at the end of the observation period. HRs were calculated in an unadjusted model (model 1); after adjustment for age, sex, race, study site, and education level (model 2); and after adjustment for additional potential confounders including body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), smoking status, physical activity, total cholesterol, high-density lipoprotein (HDL) cholesterol, and fasting glucose (model 3). Covariates were selected a priori because they have been shown to be associated with BP and CVD events.[1,2,13] We adjusted for covariates that were obtained at the examination closest to, but not after, age 40 years for each participant. We tested for heterogeneity in the association between BP and outcomes by sex or race with the inclusion of multiplicative interaction terms. After fitting Cox regression models, we tested the proportional hazards assumption of each BP group on the basis of Schoenfeld residuals.[14] If the proportional hazards assumption was violated, we plotted log-log Kaplan-Meier curves of each BP group to check the points where the curves crossed.

In a sensitivity analysis, to refine the BP groups by requiring 2 or more BP readings for classification of BP stage, participants were categorized as having (1) normal BP at every examination, (2) elevated BP at 2 or more examinations and SBP/DBP less than 130/80 mm Hg at all examinations, (3) stage 1 hypertension at 2 or more examinations and SBP/DBP less than 140/90 mm Hg at all examinations, and (4) stage 2 hypertension at 2 or more examinations. We excluded 119 participants with elevated BP or stage 1 or 2 hypertension at only a single examination from this analysis. All statistical analyses were performed with STATA (StataCorp), version 12.1. Statistical significance was defined as a *P* value less than .05 using 2-sided tests.

Results

Of the 5115 participants, we excluded 1 participant who withdrew study consent, 19 participants who experienced CVD events before 40 years of age, 13 participants who were lost to follow-up, 220 participants who had BP measurements from only a single examination, and 11 participants who had any missing covariates. The final analytical sample size was 4851 participants (mean age when follow-up began, 35.7 years [SD, 3.6]; 2657 women [55%]; 2441 African American [50%]; 206 taking antihypertensive medication when follow-up began [4%]). The flow diagram illustrating the derivation of the sample for the analyses is shown in eFigure 2 in the Supplement. Using BP obtained at 2 or more clinic visits (mean, 5.0 visits [SD, 1.1]) before age 40 years over a median of 10.7 years (interquartile range [IQR], 8.2-15.5), the

Table 1. Characteristics of Participants in the CARDIA Study at Examination Before Age 40 Years When Follow-up Time Started[a]

Characteristics	Overall (N = 4851), Mean (SD)	Blood Pressure Groups, Mean (SD)[b]			
		Normal (n = 2574)	Elevated (n = 445)	Stage 1 Hypertension (n = 1194)	Stage 2 Hypertension (n = 638)
Age, y	35.7 (3.6)	35.3 (3.9)	35.3 (3.9)	36.0 (3.2)	36.6 (2.7)
Women, No. (%)	2657 (54.8)	1743 (67.7)	145 (32.6)	471 (39.5)	298 (46.7)
Race, No. (%)					
African American	2441 (50.3)	1085 (42.2)	256 (57.5)	646 (54.1)	454 (71.2)
White	2410 (49.7)	1489 (57.8)	189 (42.5)	548 (45.9)	184 (28.8)
BMI	27.7 (6.6)	26.1 (5.7)	28.0 (5.7)	28.9 (6.7)	31.6 (8.0)
Current smokers, No. (%)	1310 (27.0)	689 (26.8)	136 (30.6)	303 (25.4)	182 (28.5)
Years of education, No.	14.6 (3.3)	14.9 (3.8)	14.4 (2.5)	14.6 (2.5)	13.9 (2.4)
Fasting glucose, mg/dL	88.6 (23.7)	85.8 (18.0)	89.2 (20.4)	89.9 (23.0)	97.3 (39.6)
Total cholesterol, mg/dL	178.9 (38.0)	174.9 (36.5)	180.8 (36.6)	182.3 (37.8)	187.1 (42.8)
HDL cholesterol, mg/dL	50.9 (14.5)	52.7 (14.1)	50.0 (13.8)	49.2 (14.8)	47.9 (14.5)
Physical activity, exercise units[c]	342.9 (283.4)	335.5 (273.7)	408.7 (304.6)	360.5 (300.9)	293.5 (261.7)
Receiving antihypertensive medication, No. (%)	206 (4.3)	0	0	0	206 (32.3)
SBP, mm Hg	110.7 (13.2)	103.2 (7.8)	114.4 (8.1)	116.4 (9.3)	128.3 (16.1)
DBP, mm Hg	72.2 (10.8)	66.3 (7.2)	70.1 (6.6)	77.7 (7.2)	86.8 (11.9)
No. of clinic visits from baseline examination to examination when follow-up began	5.0 (1.1)	4.8 (1.2)	5.1 (1.0)	5.1 (1.1)	5.2 (1.1)
Duration from baseline examination to examination when follow-up began, median (IQR), y	10.7 (8.2-15.5)	10.6 (7.9-15.3)	10.8 (10.3-15.5)	10.7 (10.2-15.6)	10.9 (10.3-15.7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

SI conversion factors: To convert HDL and total cholesterol to mmol/L, multiply by 0.0259; glucose to mmol/L, multiply by 0.0555.

[a] The date when follow-up began was defined as the date of the examination that occurred closest to, but not after, age 40 y for each participant.

[b] Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg); elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg); or stage 2 hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medication).

[c] Physical activity was assessed with the CARDIA Physical Activity History questionnaire, and the method for calculating exercise units is described in the Supplement.

4851 participants were categorized as having normal BP (n = 2574), elevated BP (n = 445), stage 1 hypertension (n = 1194), and stage 2 hypertension (n = 638).

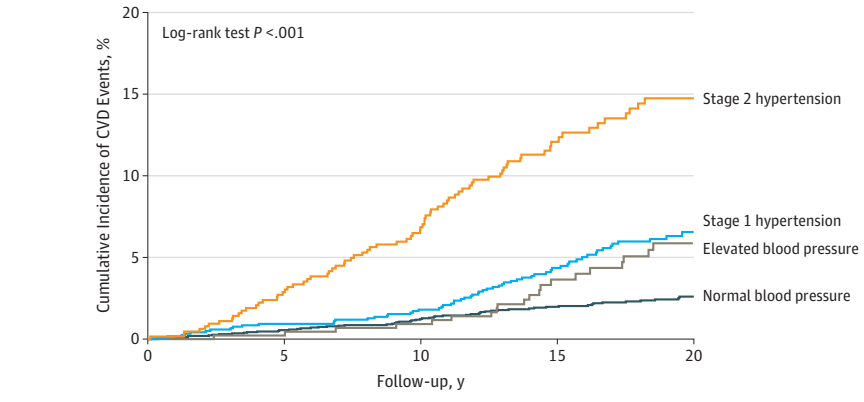
Participants with elevated BP, stage 1 hypertension, and stage 2 hypertension before age 40 were older, less likely to be women, and more likely to be African American than their counterparts with normal BP (**Table 1**). At the Y_0 examination and when follow-up started, participants in the stage 1 and 2 hypertension groups had higher BMI levels, lower education levels, higher glucose and total cholesterol levels, and lower HDL cholesterol levels compared with the normal BP group (Table 1; eTable 1 in the Supplement).

Primary Analysis

During a median follow-up of 18.8 years (IQR, 14.1-20.2), 228 CVD events (CHD, 109; stroke, 63; heart failure, 48; peripheral artery disease, 8) and 319 all-cause deaths occurred. All CVD events and deaths occurred before age 60 years. The cumulative incidence of CVD events was highest in the stage 2 hypertension group, followed by the stage 1 hypertension group, the elevated BP group, and the normal BP group (**Figure 1**). The event rates for CVD events per 1000 person-years were highest in the stage 2 hypertension group (8.04 [95% CI, 6.45-10.03]), followed by the stage 1 hypertension group (3.15 [95% CI, 2.47-4.02]), the elevated BP group (2.74 [95% CI, 1.78-4.20]), and the normal BP group (1.37 [95% CI, 1.07-1.75]) (**Table 2**). In an unadjusted model, elevated BP (HR, 2.01 [95% CI, 1.22-3.28]), stage 1 hypertension (HR, 2.31 [95% CI, 1.63-3.27]), and stage 2 hypertension (HR, 6.03 [95% CI, 4.33-8.40]) were associated with a significantly higher risk of CVD events compared with normal BP (Table 2). After multivariable adjustment, the HRs (95% CIs) for CVD events were 1.67 (95% CI, 1.01-2.77) for elevated BP, 1.75 (95% CI, 1.22-2.53) for stage 1 hypertension, and 3.49 (95% CI, 2.42-5.05) for stage 2 hypertension before age 40, respectively.

The proportional hazards assumption tests in model 3 suggested that only the elevated BP group violated the proportional hazards assumption ($P < .01$). Log-log Kaplan-Meier curves of the normal BP group and the elevated BP group crossed around a follow-up period of 10 years. For the first 10 years of follow-up, CVD event rates per 1000 person-years were 0.92 for the elevated BP group and 1.23 for the normal BP groups, and the HR (95% CI) for CVD events for

Figure 1. Cumulative Incidence of Cardiovascular Disease (CVD) Events Among Participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study by Blood Pressure (BP) Group



No. at risk					
Blood pressure					
Normal	2574	2522	2351	1824	813
Elevated	445	437	409	286	99
Hypertension					
Stage 1	1194	1158	1078	732	284
Stage 2	638	603	519	314	105

The cumulative probability of CVD events by BP groups were calculated using the Kaplan-Meier method. Log-rank test was used to calculate *P* value, and the value was less than .001. Participants were categorized as having normal BP (untreated systolic BP [SBP] <120 mm Hg and diastolic BP [DBP] <80 mm Hg); elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg); or stage 2 hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medication). The median length of follow-up for each group was as follows: normal BP, 19.1 (interquartile range [IQR], 14.5-21.0); elevated BP, 18.6 (IQR, 14.1-19.8); stage 1 hypertension, 18.7 (IQR, 14.0-19.9); and stage 2 hypertension, 14.9 (IQR, 13.0-19.4).

Table 2. The Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios (HRs) for Cardiovascular Disease (CVD) Events Among Participants in the CARDIA Study by Blood Pressure Group

	Blood Pressure Groups, HR (95% CI)[b]				
CVD Events (n = 228)[a]	Normal (n = 2574)	Elevated (n = 445)	Stage 1 Hypertension (n = 1194)	Stage 2 Hypertension (n = 638)	*P* Value for Trend
No. of events	64	21	64	79	
Incidence rate (95% CI)[c]	1.37 (1.07-1.75)	2.74 (1.78-4.20)	3.15 (2.47-4.02)	8.04 (6.45-10.03)	
Model 1 (unadjusted)	1 [Reference]	2.01 (1.22-3.28)	2.31 (1.63-3.27)	6.03 (4.33-8.40)	<.001
Model 2[d]	1 [Reference]	1.70 (1.03-2.82)	1.86 (1.30-2.67)	4.36 (3.07-6.20)	<.001
Model 3[e]	1 [Reference]	1.67 (1.01-2.77)	1.75 (1.22-2.53)	3.49 (2.42-5.05)	<.001

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a] CVD events included coronary heart disease, hospitalization for heart failure, stroke, transient ischemic attack, or intervention for peripheral artery disease.

[b] Participants were categorized as having normal blood pressure (untreated SBP <120 mm Hg and DBP <80 mm Hg); elevated blood pressure (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg); or stage 2 hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medication).

[c] The incidence rate was per 1000 person-years.

[d] Model 2 included adjustment for age when follow-up time started, race, sex, educational level, and study site (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; or Oakland, California).

[e] Model 3 included the variables in Model 2 and clinical and behavioral characteristics when follow-up time started (body mass index, smoking status, physical activity, total cholesterol, high-density lipoprotein cholesterol, and fasting glucose).

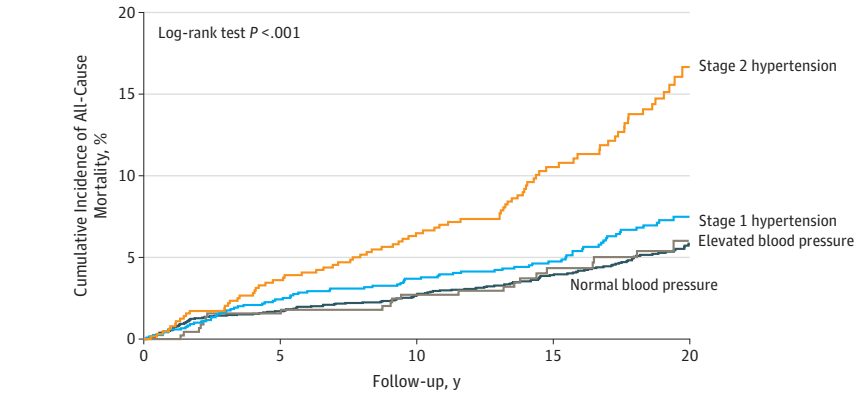
elevated BP was not statistically significant (HR, 0.55 [95% CI, 0.19-1.59]). During the remaining years of follow-up, CVD event rates per 1000 person-years were higher in the elevated BP group (2.29) than in the normal BP group (0.73), and the HR (95% CI) for CVD events for the elevated BP group was 2.99 (95% CI, 1.63-5.48).

Cumulative all-cause mortality was higher in the stage 2 hypertension group compared with other BP groups (**Figure 2**). The stage 1 hypertension group had higher cumulative all-cause mortality compared with the elevated BP and normal BP groups. The mortality rates per 1000 person-years were highest in the stage 2 hypertension group (7.96 [95% CI, 6.41-9.89]), followed by the stage 1 hypertension group (3.67 [95% CI, 2.93-4.60]), the elevated BP group (3.22 [95% CI, 2.18-4.77]), and the normal BP group (2.89 [95% CI, 2.44-3.42]) (**Table 3**). In an unadjusted model comparing with normal BP as the referent, stage 2 hypertension before age 40 years was associated with a significantly higher risk of all-cause mortality (HR, 2.82 [95% CI, 2.14-3.71]). This association remained after adjusting for covariates. Elevated BP and stage 1 hypertension were not associated with a higher risk for mortality compared with normal BP. The proportional hazards assumption tests in model 3 yielded no violation (all $P > .10$). There was no evidence of interaction between BP and race or sex in association with CVD events or all-cause mortality (all $P > .10$).

Sensitivity Analysis

When participants were categorized in BP groups defined using 2 or more visits with SBP and DBP levels in a category, CVD

Figure 2. Cumulative Incidence of All-Cause Mortality Among Participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study by Blood Pressure (BP) Group



No. at risk					
Blood pressure					
Normal	2574	2530	2371	1851	829
Elevated	445	438	411	294	102
Hypertension					
Stage 1	1194	1165	1094	764	297
Stage 2	638	615	549	347	113

The cumulative probability of all-cause mortality by BP groups were calculated using the Kaplan-Meier method. Log-rank test was used to calculate *P* value, and the value was less than .001. Participants were categorized as having normal BP (untreated systolic BP [SBP] <120 mm Hg and diastolic BP [DBP] <80 mm Hg); elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg); or stage 2 hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medication). The median length of follow-up for each group was as follows: normal BP, 19.1 (interquartile range [IQR], 14.6-21.1); elevated BP, 18.7 (IQR, 14.2-19.9); stage 1 hypertension, 18.8 (IQR, 14.2-20.0); and stage 2 hypertension, 17.6 (IQR, 13.7-19.6).

Table 3. The Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios (HRs) for All-Cause Mortality Among Participants in the CARDIA Study by Blood Pressure Group

	Blood Pressure Groups, HR (95% CI)[a]				
All-Cause Mortality (n = 319)	Normal (n = 2574)	Elevated (n = 445)	Stage 1 Hypertension (n = 1194)	Stage 2 Hypertension (n = 638)	*P* Value for Trend
No. of events	136	25	76	82	
Incidence rate (95% CI)[b]	2.89 (2.44-3.42)	3.22 (2.18-4.77)	3.67 (2.93-4.60)	7.96 (6.41-9.89)	
Model 1 (unadjusted)	1 [Reference]	1.13 (0.74-1.73)	1.29 (0.97-1.70)	2.82 (2.14-3.71)	<.001
Model 2[c]	1 [Reference]	0.91 (0.59-1.40)	1.13 (0.84-1.51)	2.32 (1.73-3.12)	<.001
Model 3[d]	1 [Reference]	0.94 (0.61-1.46)	1.15 (0.86-1.55)	2.19 (1.61-2.99)	<.001

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a] Participants were categorized as having normal blood pressure (untreated SBP <120 mm Hg and DBP <80 mm Hg); elevated blood pressure (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg); or stage 2 hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medication).

[b] The incidence rate was per 1000 person-years.

[c] Model 2 included adjustment for age when follow-up time started, race, sex, educational level, and study site (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; or Oakland, California).

[d] Model 3 included the variables in Model 2 and clinical and behavioral characteristics when follow-up time started (body mass index, smoking status, physical activity, total cholesterol, high-density lipoprotein cholesterol, and fasting glucose).

event rates per 1000 person-years (eTable 2 in the Supplement) were highest in the stage 2 hypertension group (9.16 [95% CI, 6.61-12.70]), followed by the elevated BP group (5.59 [95% CI, 3.65-8.58]), the stage 1 hypertension group (4.23 [95% CI, 3.14-5.70]), and the normal BP group (1.84 [95% CI, 1.54-2.20]). After multivariable adjustment, the HRs for CVD events for elevated BP, stage 1 hypertension, and stage 2 hypertension vs normal BP before age 40 were 2.44 (95% CI, 1.50-3.96), 1.52 (95% CI, 1.05-2.20), and 3.09 (95% CI, 2.07-4.61), respectively (eTable 2, top panel, in the Supplement). In an unadjusted model, stage 1 hypertension (HR, 1.59 [95% CI, 1.16-2.19]) and stage 2 hypertension (HR, 3.38 [95% CI, 2.41-4.74]) were significantly associated with all-cause mortality (eTable 2, bottom panel, in the Supplement). After multivariable adjustment, stage 2 hypertension was associated with a significantly higher risk of all-cause mortality compared with normal BP (HR, 2.82 [95% CI, 1.95-4.09]).

Post Hoc Analysis

During follow-up, the following CVD events occurred: CHD, 114; stroke, 72; transient ischemic attack, 2; heart failure, 66; and peripheral artery disease, 9. The sum of these events (263 events) exceeds the 228 CVD events used in the primary analysis because 30 participants had more than 1 type of events. Event rates and HRs for CHD and stroke events were highest in the stage 2 hypertension group, second-highest in the stage 1 hypertension and elevated BP

groups, and lowest in the normal BP group (eTable 3, upper and middle panels, in the Supplement). The event rates and HRs followed a dose-response relationship across stages of hypertension for heart failure events (eTable 3, bottom panel, in the Supplement). The proportional hazards assumption tests of each BP group in all models yielded no violation (all $P > .10$).

Discussion

In this community-based study of African American and white participants, there was an association between BP before age 40 years, categorized using the BP classification scheme of the 2017 ACC/AHA BP guideline, and incident CVD events and all-cause mortality by middle age. Elevated BP, stage 1 hypertension, and stage 2 hypertension at any time before age 40 years were each associated with a significantly higher risk for CVD events compared with maintaining normal BP. The higher CVD risk associated with elevated vs normal BP was evident after the initial 10 years of follow-up. Stage 2 hypertension was associated with a significantly higher risk for all-cause mortality compared with normal BP.

Prior studies have shown prospective associations between clinic-measured BP classification in young adulthood and later-life CVD events in the United States.[15-19] In the Build and Blood Pressure Study,[15] which included adults aged 30 to 39 years, an SBP more than 115 mm Hg and DBP more than 75 mm Hg were associated with an increased risk for mortality. Data from 148 204 men aged 35 to 44 years who were screened for the Multiple Risk Factor Intervention Trial (MRFIT)[16] showed that the age-adjusted CVD event rate was 8.8 per 10 000 person-years for men with an SBP less than 120 mm Hg and DBP less than 80 mm Hg, 14.1 for men with an SBP of 120 mm Hg to 129 mm Hg and DBP of 80 mm Hg to 84 mm Hg, and 18.4 for men with an SBP of 130 mm Hg to 139 mm Hg and DBP of 85 mm Hg to 89 mm Hg.

In these prior studies, BP measured at a single occasion was used for BP classification, which might not fully reflect a person's BP phenotype in young adulthood. For example, a prior CARDIA study[20] showed that 30% to 50% of young adults with an SBP of 130 mm Hg to 139 mm Hg had an SBP of 140 mm Hg or more or DBP of 90 mm Hg or more over the next 5 years. The BP classification used in the current study was defined with BP measurements obtained from at least 2 clinic visits (mean 5.0 visits [SD, 1.1]) over a median period of 10.7 years. This approach might minimize the potential misclassification effect of progression to higher BP categories from stage 1 hypertension on cardiovascular outcomes associated with stage 1 hypertension. Furthermore, in the prior studies, participants were recruited until 1980, before the onset of the obesity epidemic in the United States.[21] Therefore, the prior studies may underestimate the effect of the obesity epidemic on BP and BP-related outcomes.

Although participants with stage 1 hypertension in the current study had a significantly higher HR for CVD than their counterparts with normal BP, their absolute risk was low. However, the lifetime risk for CVD events among young adults with stage 1 hypertension may be high.[22] Prior CARDIA studies have suggested that young adults with an SBP of 120 mm Hg to 139 mm Hg or DBP of 80mm Hg to 89 mm Hg had greater coronary artery calcium and a higher prevalence of left ventricular hypertrophy in midlife compared with counterparts who maintained normal BP.[23,24] The high prevalence of subclinical CVD might be explained by individuals' higher cumulative exposure to BP from young adulthood to midlife.[23,24]

Antihypertensive medication in middle-aged and older adults does not completely mitigate the higher CVD risk among those with high BP compared with their counterparts who maintain normal BP without taking antihypertensive medication.[25] Nonpharmacological and pharmacological interventions in young adults with elevated BP or stage 1 hypertension should lower cumulative exposure to elevated BP from young adulthood to later life, which in turn may reduce the lifetime risk of CVD.[26]

Most large-scale outcomes trials of antihypertensive medication enrolled middle-aged and older adults. Studies are needed to determine the optimal antihypertensive treatment strategy for young adults with hypertension (eg, when antihypertensive medication should be started, the effectiveness of low-dose antihypertensive therapy, and the optimal BP treatment goal). Pharmacological treatment with unclear benefit-to-harm ratios over a lifetime may be impractical for young adults. Randomized clinical trials are needed to determine if a treatment benefit can be achieved over a short to moderate time frame in some subgroups of young adults with stage 1 hypertension. Enrolling young adults with a high lifetime risk for CVD may be practical. Because of the consequent amount of time that must pass to accumulate a sufficient number of CVD events, studies of young adults that could use subclinical CVD markers (eg, left ventricular hypertrophy, coronary artery calcium) as primary outcomes would be an initial step toward providing evidence that pharmacological treatments are appropriate for young adults with hypertension.

Strengths of this study include the large, community-based cohort of white and African American participants; adjudication of suspected cardiovascular outcomes by a panel of physicians using detailed evaluation criteria; high retention; and the standardized data collection protocols and rigorous quality control in this study. The inception of this study was in 1985, widely recognized as the inflection point in the American obesity epidemic.[21] Because of the young age of the participants in this study at inception, all events in these analyses are considered to be premature CVD events and deaths, an important measure of a population's health unavailable in older cohorts.

Limitations

This study has several limitations. First, possible residual confounding, including sodium intake and psychological factors, may be affecting the BP-CVD event associations.[27,28]

Second, it remains unclear how BP measurements in this study collected in a highly controlled research setting correspond to BP measurements commonly obtained in a typical clinic setting. Third, antihypertensive medication use by participants younger than 40 years in this study might be higher than usage levels in the general population.[29] Although the reason is unclear, the difference might result from research participation effects (ie, the Hawthorne effect).[30] Fourth, our results may not be generalizable to other racial and ethnic groups (eg, Asian and Hispanic).

Conclusions

Among young adults, those with elevated blood pressure, stage 1 hypertension, and stage 2 hypertension before age 40 years, as defined by the blood pressure classification in the 2017 ACC/AHA guidelines, had significantly higher risk for subsequent CVD events compared with those with normal blood pressure before age 40 years. The ACC/AHA blood pressure classification system may help identify young adults at higher risk for CVD events.

ARTICLE INFORMATION

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